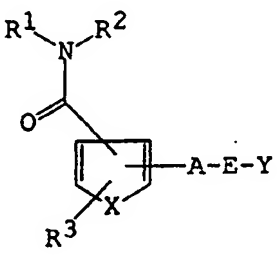





## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification <sup>6</sup> : C07D 235/08, A61K 31/415, 31/40, C07D 235/14, 235/30, 209/08, 209/42, 235/12, 235/24, 235/06, 235/10, 235/26, 209/12, 401/04, 401/06</p>	A1	<p>(11) International Publication Number: <b>WO 98/24771</b></p> <p>(43) International Publication Date: 11 June 1998 (11.06.98)</p>
<p>(21) International Application Number: PCT/JP97/04192</p> <p>(22) International Filing Date: 18 November 1997 (18.11.97)</p> <p>(30) Priority Data: PO 3953 2 December 1996 (02.12.96) AU</p> <p>(71) Applicant (for all designated States except US): FUJISAWA PHARMACEUTICAL CO., LTD. [JP/JP]; 4-7, Doshomachi 3-chome, Chuo-ku, Osaka-shi, Osaka 541 (JP).</p> <p>(72) Inventors; and</p> <p>(75) Inventors/Applicants (for US only): SETOI, Hiroyuki [JP/JP]; 4-13-1, Namiki, Tsukuba-shi, Ibaraki 305 (JP). OHKAWA, Takehiko [JP/JP]; 944-2, Mukoishige, Ishigemachi, Yuki-gun, Ibaraki 300-27 (JP). ZENKOH, Tatsuya [JP/JP]; 6-3-3-A101, Keyakidai, Moriyamachi, Kitasouma-gun, Ibaraki 302-01 (JP). SAWADA, Hitoshi [JP/JP]; 2-25-10, Matsushiro, Tsukuba-shi, Ibaraki 305 (JP). SAWADA, Yuki [JP/JP]; 2-28-40, Kamikashiwada, Ushiku-shi, Ibaraki 300-12 (JP). OKU, Teruo [JP/JP]; 8-2, Midorigaoka, Tsukuba-shi, Ibaraki 305 (JP).</p>		<p>(74) Agent: SEKI, Hideo; Fujisawa Pharmaceutical Co., Ltd., Osaka Factory, 1-6, Kashima 2-chome, Yodogawa-ku, Osaka-shi, Osaka 532 (JP).</p> <p>(81) Designated States: AU, CA, CN, HU, IL, JP, KR, MX, US, Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).</p> <p><b>Published</b> <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>
<p>(54) Title: BENZAMIDE DERIVATIVES HAVING A VASOPRESSIN ANTAGONISTIC ACTIVITY</p> <p>(57) Abstract</p> <p>This invention relates to new benzamide derivatives having a vasopressin antagonistic activity, etc. and represented by general formula (I) wherein R<sup>1</sup> is aryl optionally substituted with lower alkoxy, etc., R<sup>2</sup> is lower alkyl, etc., R<sup>3</sup> is hydrogen etc., A is NH, etc., E is (a), etc., X is -CH=CH-, -CH=N-, or S, and Y is a condensed heterocyclic group, etc., and pharmaceutically acceptable salts thereof, to processes for preparation thereof and to a pharmaceutical composition comprising the same.</p> <div style="display: flex; align-items: center; justify-content: center;"> <div style="text-align: center;">  <p>(I)</p> </div> <div style="margin-left: 20px;"> <p>(a)</p>  </div> </div>		

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## DESCRIPTION

## BENZAMIDE DERIVATIVES HAVING A VASOPRESSIN ANTAGONISTIC ACTIVITY

## 5 TECHNICAL FIELD

This invention relates to new benzamide derivatives and pharmaceutically acceptable salts thereof which are useful as a medicament.

## 10 BACKGROUND ART

Some benzamide derivatives have been known as vasopressin antagonist, for example, in PCT International Publication Nos. WO 91/05549, WO 95/29152 and WO 96/41795, and EP Application Publication No. 0620216.

15

## DISCLOSURE OF INVENTION

This invention relates to new benzamide derivatives and pharmaceutically acceptable salts thereof.

More particularly, it relates to new benzamide  
20 derivatives and pharmaceutically acceptable salts thereof which possess activities as vasopressin antagonistic activity, vasodilating activity, hypotensive activity, activity for inhibiting saccharide release in liver, activity for inhibiting growth of mesangium cells, water diuretic  
25 activity, platelet agglutination inhibitory activity, oxytocin antagonistic activity and the like, to a pharmaceutical composition comprising the salt and to a method for the treatment and/or prevention of hypertension, heart failure, renal insufficiency, edema, ascites,  
30 vasopressin parasecretion syndrome, hepatocirrhosis, hyponatremia, hypokalemia, diabetic, circulation disorder, cerebrovascular disease (e.g. cerebral edema, cerebral infarction, etc.), Meniere's syndrome (e.g. Meniere's disease, etc.), motion sickness and the like in human beings  
35 or animals.

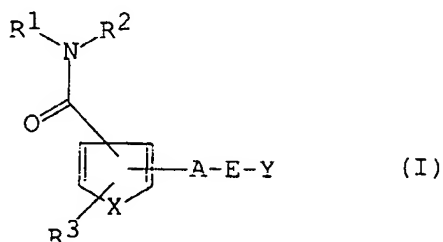
One object of this invention is to provide new and useful benzamide derivatives which possess aforesaid activities.

Another object of this invention is to provide processes for the preparation of said benzamide derivatives and salts thereof.

A further object of this invention is to provide a pharmaceutical composition comprising, as an active ingredient, said benzamide derivatives and pharmaceutically acceptable salts thereof.

Still further object of this invention is to provide a therapeutical method for the treatment and/or prevention of aforesaid diseases in human beings or animals, using said benzamide derivatives and pharmaceutically acceptable salts thereof.

The object benzamide derivatives of this invention are new and can be represented by the following general formula (I) :



wherein

$R^1$  is aryl, cyclo(lower)alkyl or a heterocyclic group, each of which may be substituted with substituent(s) selected from the group consisting of halogen; hydroxy; nitro; protected amino; amino; acyl; substituted acyl; acyl(lower)alkylsulfinyl; acyl(lower)alkylsulfonyl; acyloxy; lower alkylamino(lower)alkylcarbamoyloxy; aryl; cyano; a heterocyclic group;



- lower alkenyl optionally substituted with acyl, substituted acyl, aryl or acyl-substituted aryl;  
 lower alkynyl optionally substituted with amino, acylamino or substituted acylamino;
- 5 lower alkyl optionally substituted with halogen, amino, lower alkylamino, acylamino, substituted acylamino, hydroxy, acyloxy, acyl(lower)alkanoyloxy, acyl, substituted acyl, acyl(lower)alkoxyimino, aryl or acyl-substituted aryl;
- 10 lower alkylthio optionally substituted with acyl or substituted acyl;  
 alkoxy optionally substituted with aryl, substituted aryl, hydroxy, acyloxy, amino, lower alkylamino, protected amino, a heterocyclic group, acyl-substituted
- 15 pyridyl, substituted acyl-substituted pyridyl, halogen, acyl(lower)alkylamino, N-protected-acyl(lower)-alkylamino, N-acyl(lower)alkyl-N-lower alkylamino, acyl, substituted acyl, acylamino, substituted acylamino, lower alkylhydrazinocarbonylamino, hydroxyimino,
- 20 acyl(lower)alkoxyimino, substituted acyl(lower)alkoxyimino, acyl(lower)alkoxy, guanidino or N-protected guanidino; and lower alkenyloxy optionally substituted with acyl or substituted acyl;
- $R^2$  is hydrogen; lower alkyl optionally substituted with
- 25 hydroxy, aryl or acyl; or cyclo(lower)alkyl;
- $R^3$  is hydrogen; halogen; hydroxy; acyloxy; substituted acyloxy; lower alkyl optionally substituted with hydroxy or lower alkoxy; lower alkoxy optionally substituted with aryl, amino, protected amino, acyl, hydroxy, cyano
- 30 or lower alkylthio; nitro; amino; acyl; substituted acyl; or cyclo(lower)alkyloxy;
- A is a single bond, O or NH;
- E is lower alkylene, lower alkenylene,  $\text{-}\overset{\text{O}}{\parallel}\text{C-}$ ,  $\text{-}\overset{\text{O}}{\parallel}\text{S-}$ , or  
 a group of the formula :

-G-J-

in which G is lower alkylene or  $\text{-}\overset{\text{O}}{\parallel}\text{C-}$  and

5 J is O or  $\text{-}\overset{\text{R}^4}{\underset{|}{\text{N}}}\text{-}$

(wherein  $\text{R}^4$  is hydrogen or N-protective group);

X is  $\text{-CH=CH-}$ ,  $\text{-CH=N-}$  or S; and

Y is aryl which may be substituted with acyl, protected  
amino(lower)alkanoyl, protected amino and nitro, amino  
10 and nitro or diamino;  
or a condensed heterocyclic group which may be  
substituted with substituent(s) selected from the group  
consisting of halogen, acyl, lower alkoxy, hydroxy,  
guanidino, mercapto, acylamino, amino, a heterocyclic  
15 group, cyanoamino, amino(lower)alkyl(lower)alkylamino,  
lower alkylamino, lower alkylamino(lower)alkylamino,  
substituted-heterocyclic group, lower alkylhydrazino,  
aryloxy, lower alkylthio, aryl, protected amino,  
N-protected lower alkylamino(lower)alkylamino,  
20 N-protected amino(lower)alkyl( $\text{N}'$ -lower alkyl)amino,  
amino(lower)alkyl(N-lower alkyl)amino, lower  
alkylamino(lower)alkyl(N-lower alkyl)amino, lower  
alkoxy(lower)alkylamino and lower alkyl optionally  
substituted with aryl, ar(lower)alkoxy, cyano,  
25 hydroxyimino, mercapto, lower alkylamino, acyloxy,  
halogen, lower alkoxy, protected hydroxy, hydroxy, lower  
alkoxyaryl, protected amino, amino, a heterocyclic group  
or substituted heterocyclic group;

provided that when Y is phenyl which may be substituted with  
30 lower alkyl or acyl,

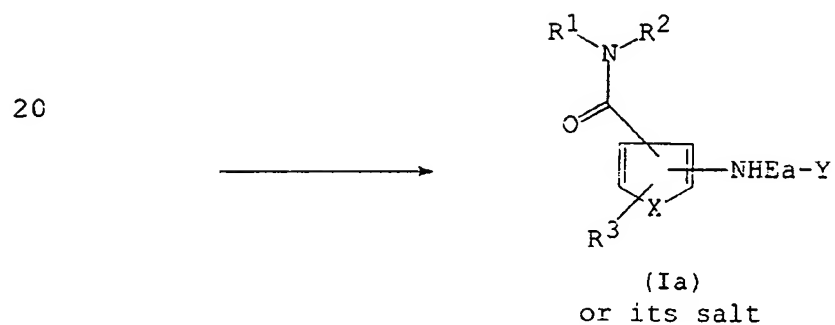
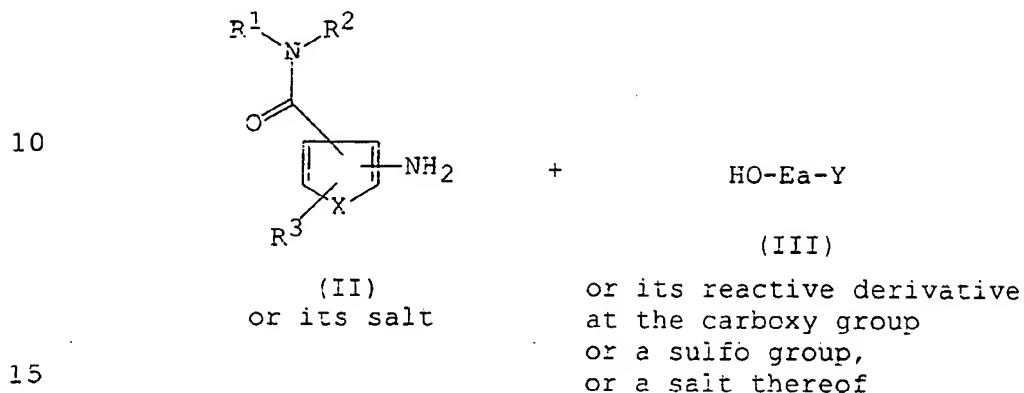
then A is a single bond and

E is  $\text{-}\overset{\text{OR}^4}{\parallel}\text{CN-}$  (wherein  $\text{R}^4$  is as defined  
above);

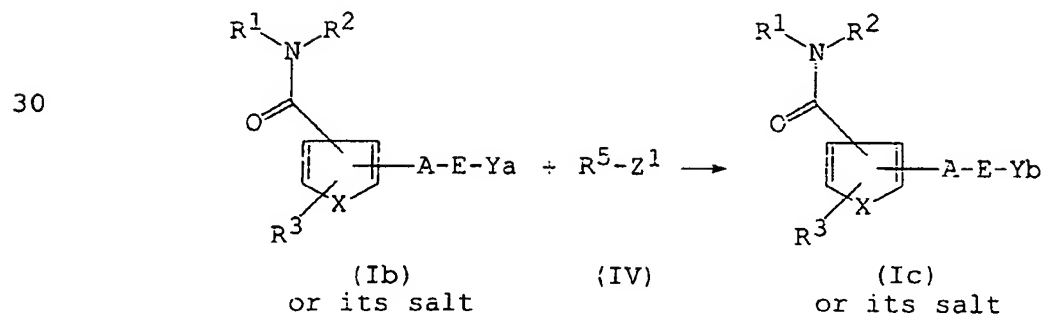
35 and pharmaceutically acceptable salt thereof.

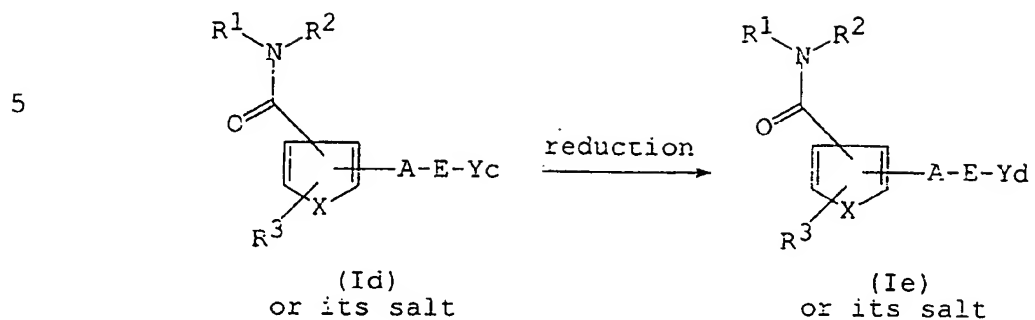
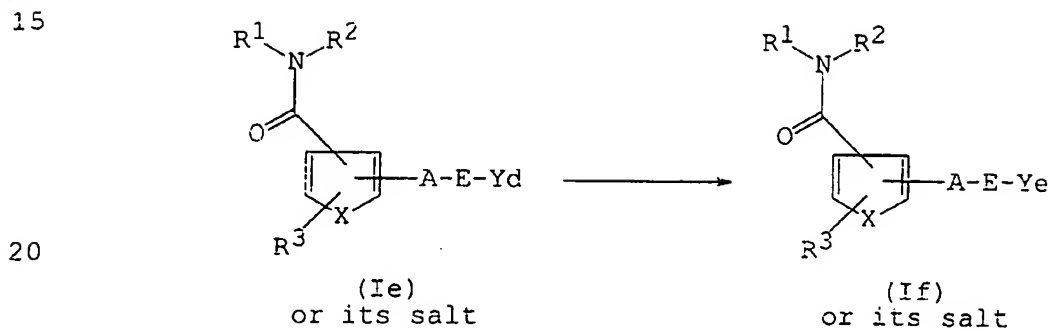
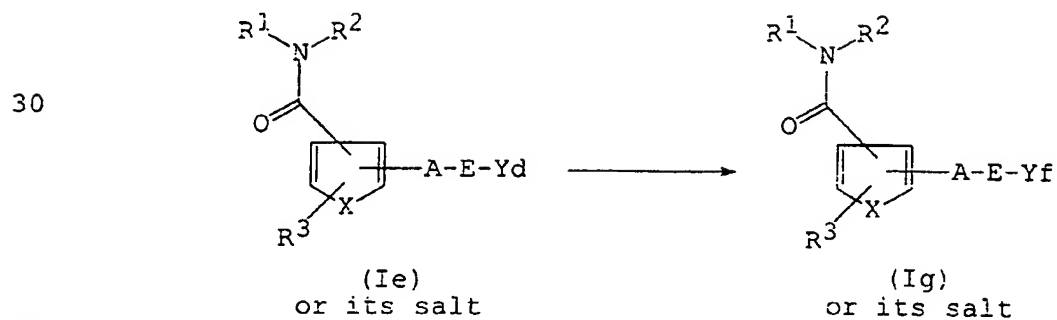
The object compound (I) or its salt can be prepared by the processes as illustrated in the following reaction schemes.

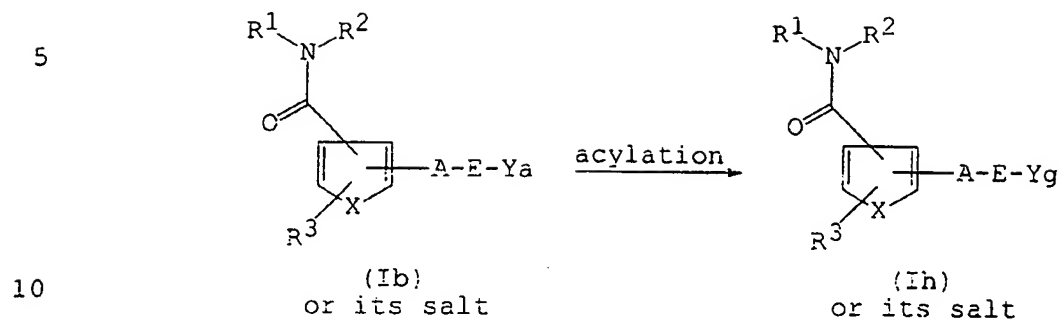
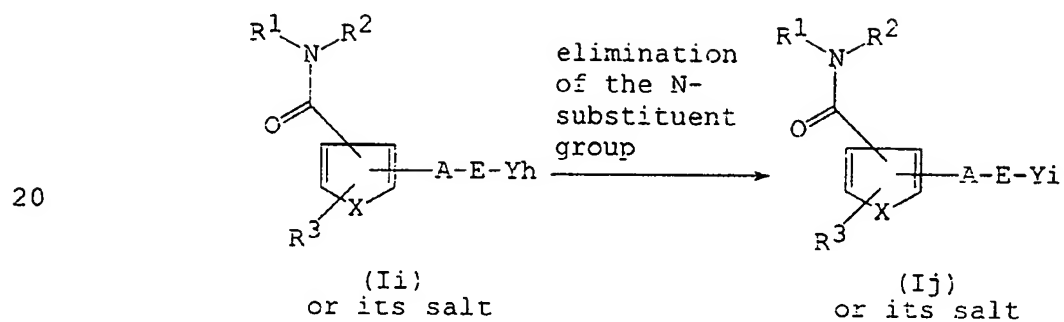
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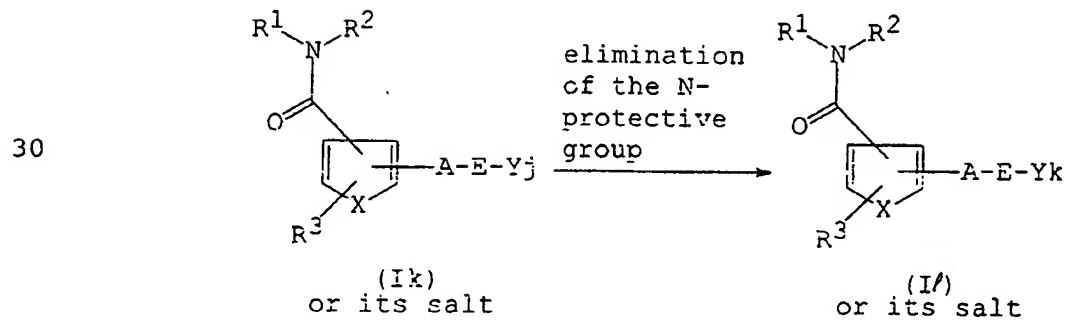
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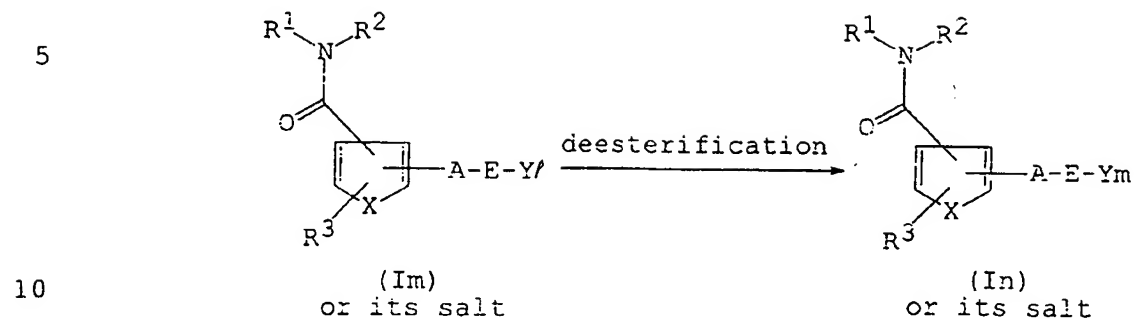
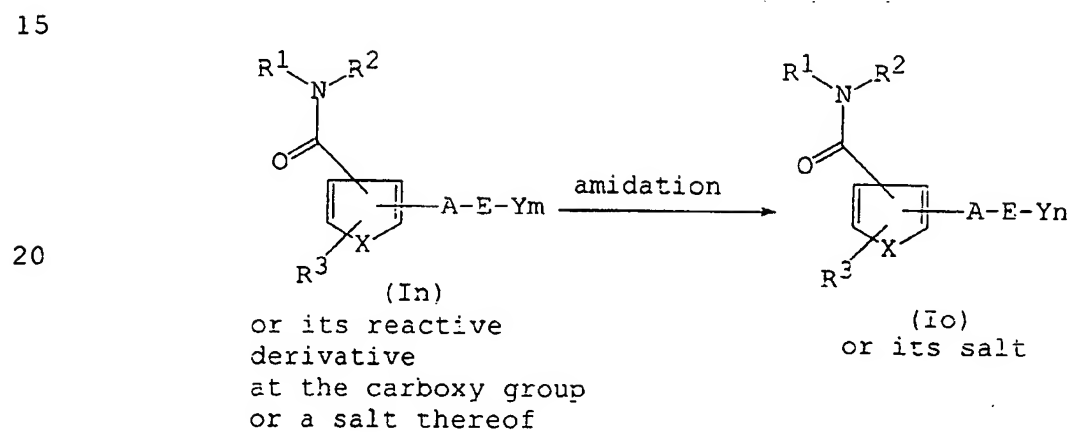
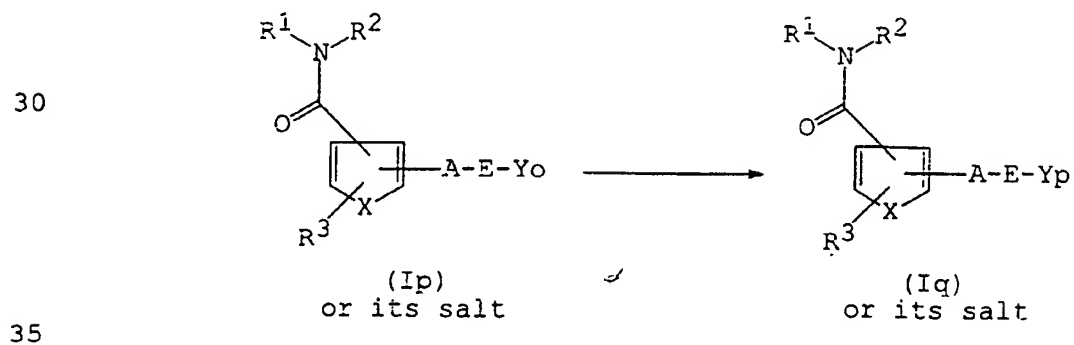


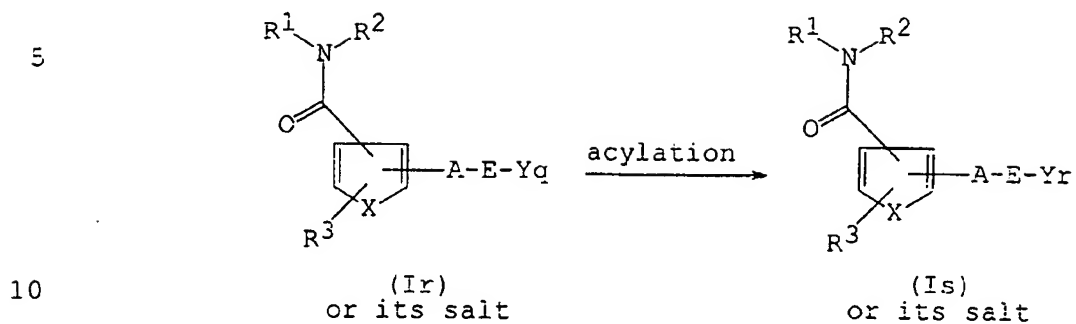
Process 3Process 4Process 5

Process 6Process 7

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Process 8

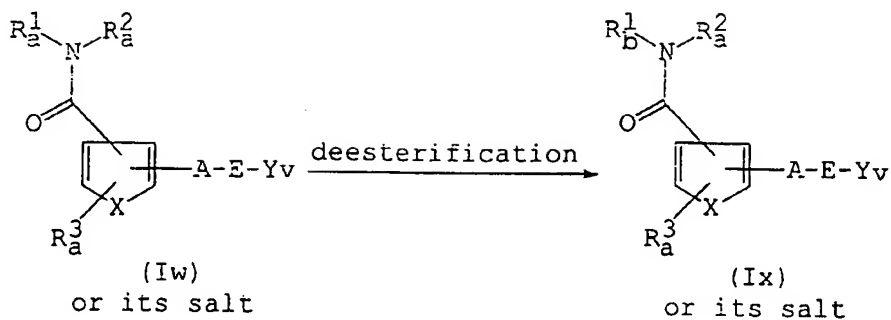
Process 9Process 10Process 11

Process 12

Process 15

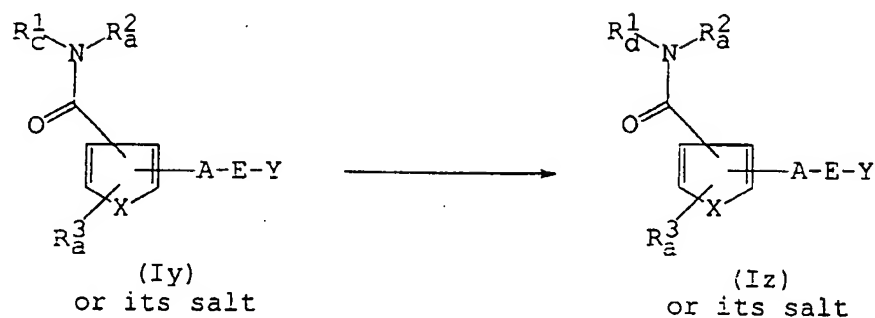
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Process 16

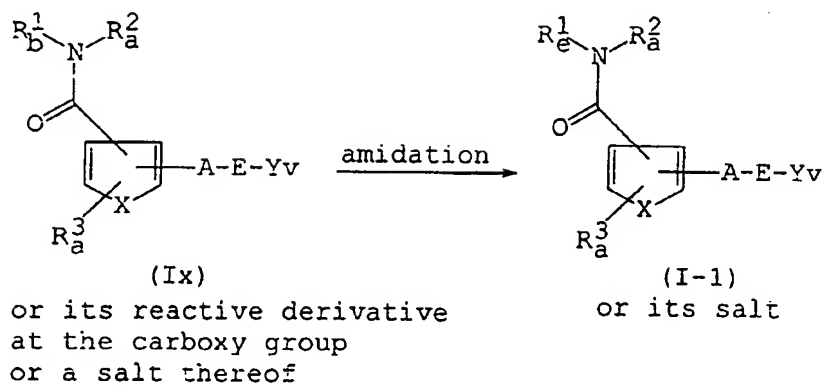
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Process 17

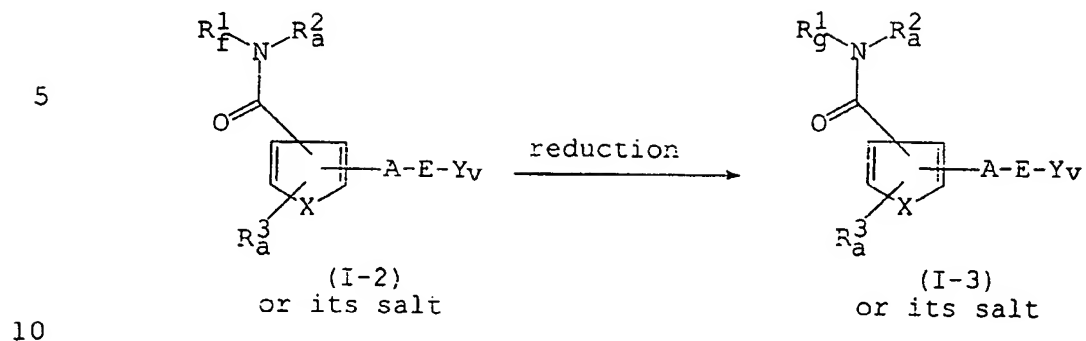
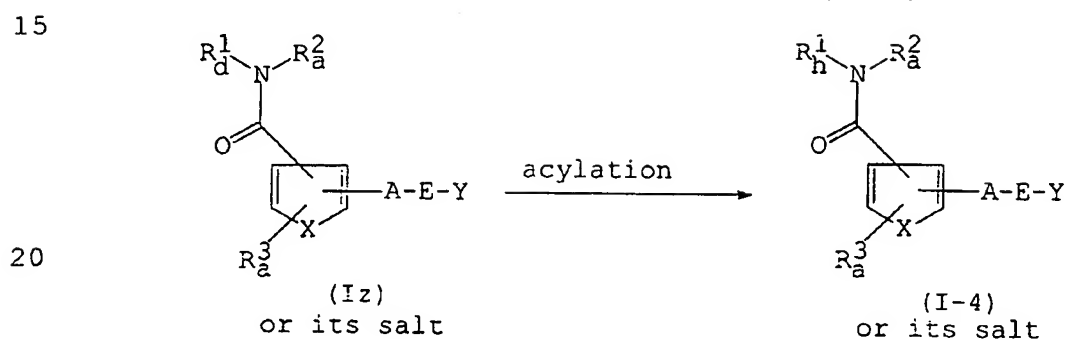
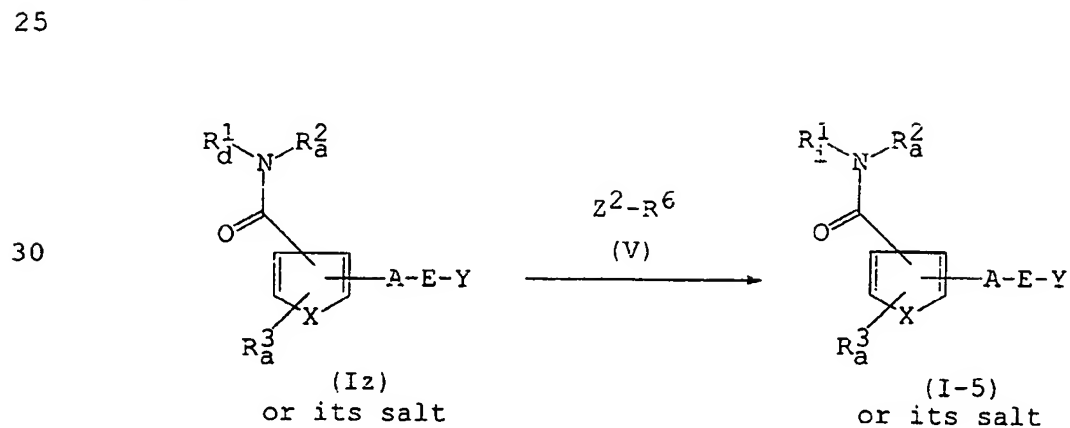
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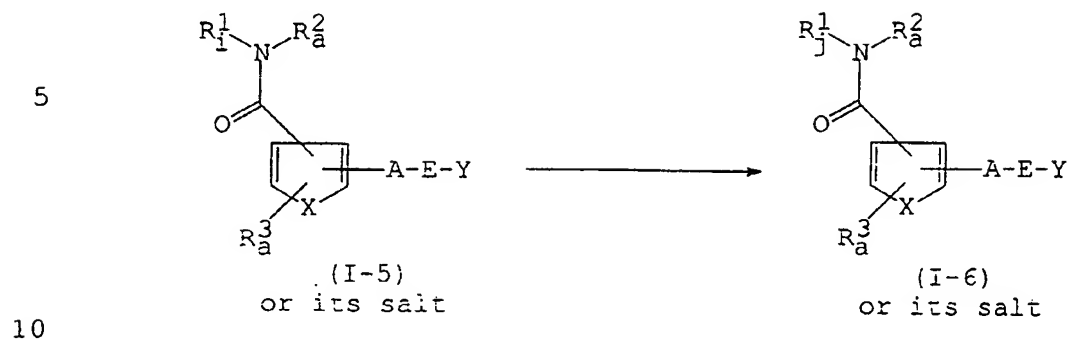
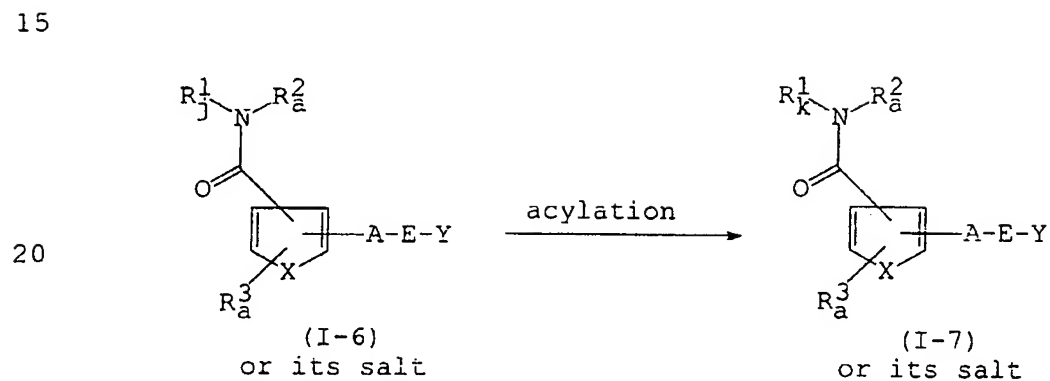
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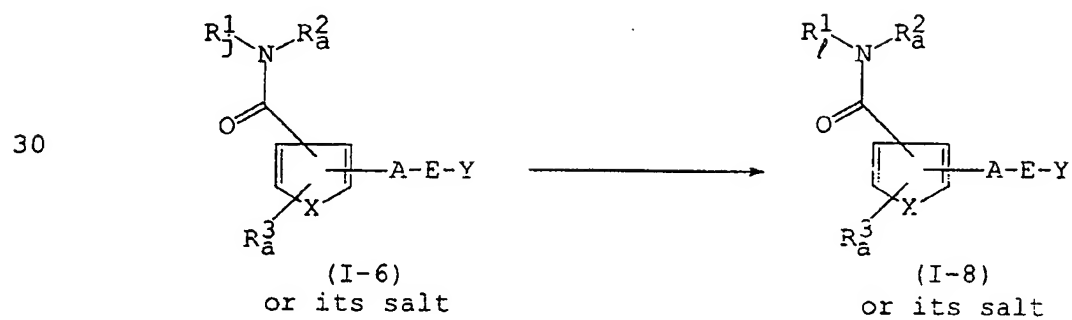
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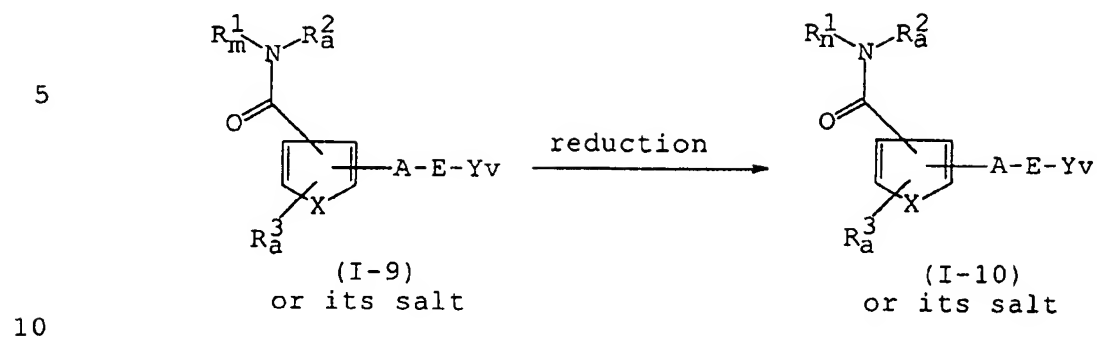
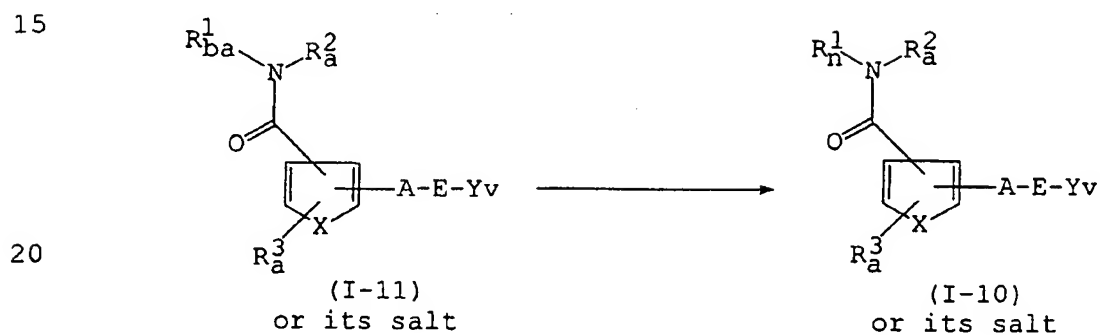
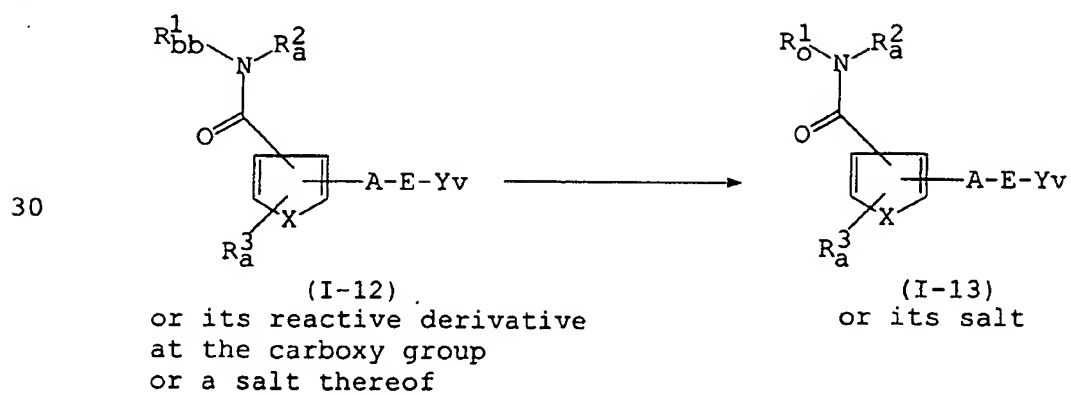


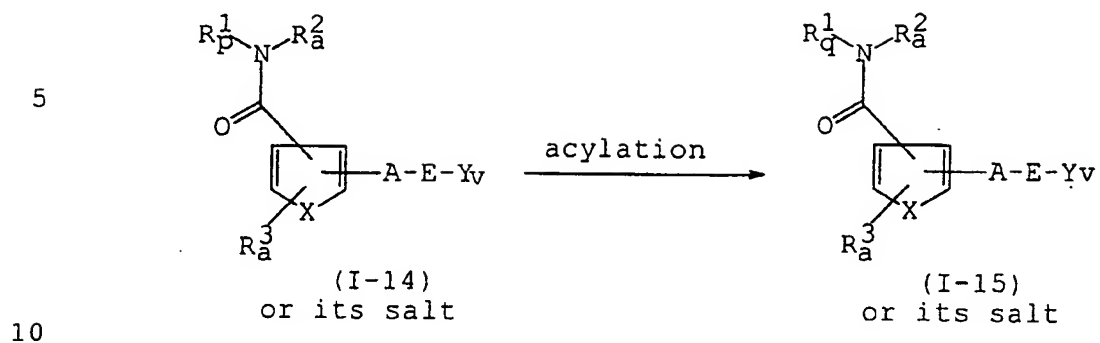
Process 18Process 19Process 20

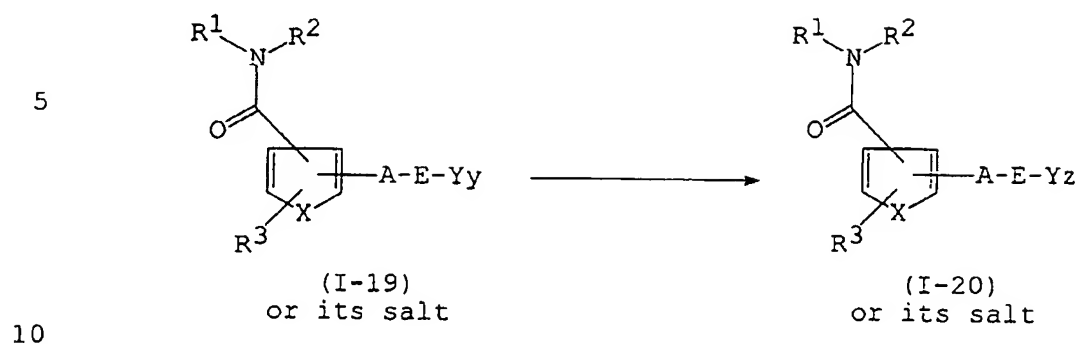
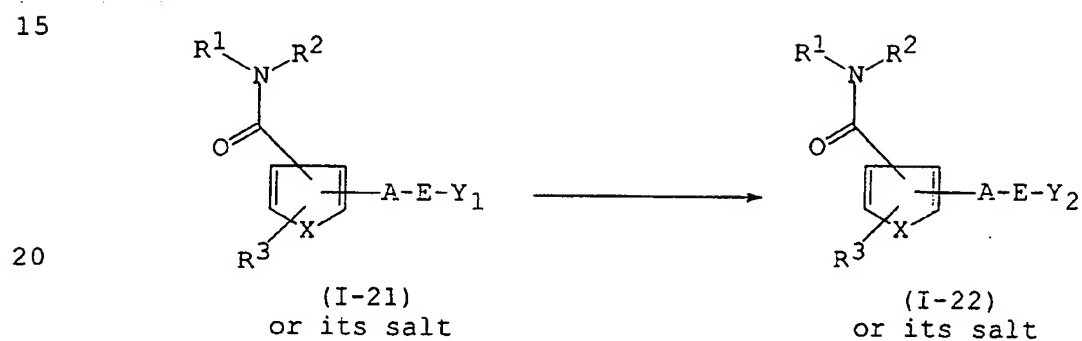
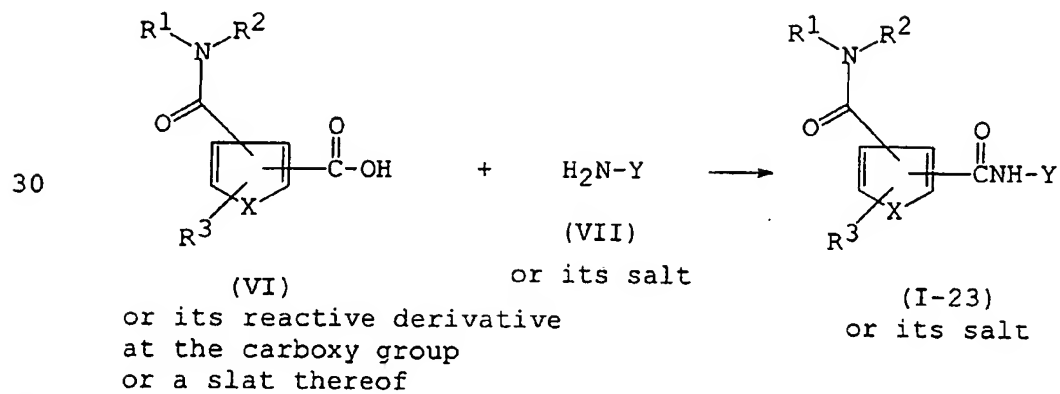
Process 21Process 22

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Process 23

Process 24Process 25Process 26

Process 27

Process 30Process 31Process 32

wherein

R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, A, E, X and Y are each as defined above,

Ea is  $\text{-}\overset{\text{O}}{\parallel}\text{C-}$  or  $\text{-}\overset{\text{O}}{\parallel}\text{S-}$ ,

Ya is indolyl,

R<sup>5</sup> is lower alkyl,

Z<sup>1</sup> is an acid residue,

Yb is N-(lower alkyl)indolyl,

Yc is phenyl substituted with amino and nitro,

Yd is phenyl substituted with diamino,

Ye is benzimidazolyl optionally 2-position substituted with aryl, phenoxy, sulfamoylamino, cyanoamino, guanidino, mercapto, amino, lower alkoxy carbonylamino, lower alkoxy or lower alkyl optionally substituted with cyano, mercapto, hydroxy, halogen, protected amino or a heterocyclic group;

Yf is quinoxalinylyl or benzotriazolyl,

Yg is N-acylindolyl,

Yh is (N-acyl)acylindolinylyl, N-acylindolinylyl, (N-acyl)hydroxy(lower)alkylindolinylyl, lower alkylamino(lower)alkylamino(N-acyl)indolinylyl, (N-lower alkoxyarylmethyl)acylbenzimidazolyl, (N-lower alkoxy carbonyl)phthalimido(lower)alkylindolyl, N-protected lower alkylamino(lower)alkylamino(N-acyl)-benzimidazolyl, (N-acyl)benzimidazolyl, (N-acyl)(lower)-alkylbenzimidazolyl, N-protected amino(lower)alkyl(N-lower alkyl)amino(N-acyl)benzimidazolyl, N-acylindolyl, (N-acyloxymethyl)indolyl, (N-acyl)acylindolyl, (N-arylmethyl)lower alkoxy(lower)alkylbenzimidazolyl or (N-lower alkoxyarylmethyl)acylbenzimidazolyl;

Yi is acylindolinylyl, indolinylyl, hydroxy(lower)alkylindolinylyl, lower alkylamino(lower)alkylaminoindolinylyl, acylbenzimidazolyl, phthalimido(lower)alkylindolyl, amino(lower)alkylindolyl, lower

- alkylamino(lower)alkylaminobenzimidazolyl,  
benzimidazolyl, lower alkylbenzimidazolyl,  
amino(lower)alkyl(N-lower alkyl)aminobenzimidazolyl,  
indolyl, acylindolyl, lower alkoxy(lower)-  
5 alkylbenzimidazolyl or acylbenzimidazolyl;  
Yj is aryl which is substituted with protected amino and  
nitro; or a condensed heterocyclic group which is  
substituted with protected amino or lower alkyl  
substituted with protected amino;  
10 Yk is aryl which is substituted with amino and nitro; or  
a condensed heterocyclic group which is substituted with  
amino or lower alkyl substituted with amino;  
Yl is aryl substituted with esterified carboxy, or  
a condensed heterocyclic group substituted with  
15 esterified carboxy,  
Ym is aryl substituted with carboxy, or a condensed  
heterocyclic group substituted with carboxy,  
Yn is aryl or a condensed heterocyclic group, each of which  
is substituted with substituted or unsubstituted  
20 N-containing heterocycliccarbonyl, carbamoyl,  
heterocycliccarbamoyl, or substituted or unsubstituted  
lower alkylcarbamoyl;  
Yo is a condensed (N-acyl)N-containing heterocyclic group or  
a condensed heterocyclic group, each of which is  
25 substituted with methoxy or lower alkyl substituted with  
protected hydroxy;  
Yp is a condensed (N-acyl)N-containing heterocyclic group or  
a condensed heterocyclic group, each of which is  
substituted with hydroxy or lower alkyl substituted with  
30 hydroxy;  
Yq is a condensed heterocyclic group which is substituted  
with amino or amino(lower)alkyl,  
Yr is a condensed heterocyclic group which is substituted  
with acylamino or acylamino(lower)alkyl,  
35 Ys is indolyl which is substituted with methyl substituted

with lower alkylamino,

Yt is a condensed heterocyclic group which is substituted  
with lower alkyl substituted with hydroxy,

Yu is a condensed heterocyclic group which is substituted  
with lower alkyl substituted with formyl,

$R_a^1$  is aryl substituted with esterified carboxy or lower  
alkoxy substituted with esterified carboxy,

$R_b^1$  is aryl substituted with carboxy or lower alkoxy  
substituted with carboxy,

$R_a^2$  is lower alkyl,

$R_a^3$  is hydrogen or lower alkoxy,

Yv is benzimidazolyl optionally substituted with lower alkyl  
or protected amino(lower)alkyl,

$R_c^1$  is aryl substituted with methoxy which is substituted with  
substituted or unsubstituted aryl,

$R_d^1$  is aryl substituted with hydroxy,

$R_e^1$  is aryl substituted with N-protected piperazinylcarbonyl,  
oxopiperidinylcarbonyl, carbamoyl, lower alkylcarbamoyl,  
lower alkylaminocarbamoyl or lower alkylamino(lower)-  
alkyl(N-lower)alkylcarbamoyl, or aryl which is  
substituted with lower alkoxy substituted with  
N-protected piperazinylcarbonyl, oxopiperidinylcarbonyl,  
carbamoyl, lower alkylcarbamoyl, lower  
alkylaminocarbamoyl or lower alkylamino(lower)alkyl(N-  
lower)alkylcarbamoyl,

$R_f^1$  is aryl which is substituted with lower alkoxy substituted  
with oxopiperidinylcarbonyl,

$R_g^1$  is aryl which is substituted with lower alkoxy substituted  
with hydroxypiperidinylcarbonyl,

$R_h^1$  is aryl substituted with acyloxy,

$R_i^1$  is aryl which is substituted with lower alkoxy substituted  
with protected amino,

$R^6$  is lower alkyl substituted with protected amino,

$Z^2$  is an acid residue,

$R_j^1$  is aryl which is substituted with lower alkoxy substituted



with amino,

$R_K^1$  is aryl which is substituted with acylamino,

$R_Y^1$  is aryl which is substituted with lower alkylamino,

$R_m^1$  is aryl substituted with nitro,

5  $R_n^1$  is aryl substituted with amino,

$R_{ba}^1$  is aryl substituted with carboxy,

$R_{bb}^1$  is aryl which is substituted with lowre alkoxy  
substituted with carboxy,

10  $R_O^1$  is aryl which is substituted with lower alkoxy substituted  
with hydroxymethyl,

$R_P^1$  is aryl which is substituted with lower alkoxy substituted  
with hydroxy,

$R_Q^1$  is aryl which is substituted with lower alkoxy substituted  
with acyloxy,

15  $R_r^1$  is aryl which is substituted with lower alkoxy substituted  
with phthalimido,

Yw is benzimidazolyl substituted with halogen,

Yx is benzimidazolyl substituted with N-lower alkylpiperidyl,  
morpholino, lower alkylamino, di(lower)alkylamino-  
20 piperidino, di(lower)alkylhydrazino,  
amino(lower)alkyl(N-lower alkyl)amino or  
di(lower)alkylamino(lower)alkylamino,

Yy is benzimidazolyl substituted with N-protected piperidyl,

Yz is benzimidazolyl substituted with piperidyl,

25  $Y_1$  is benzimidazolyl or indolyl, each of which is substituted  
with formyl or cyano(lower)alkyl, and

$Y_2$  is benzimidazolyl or indolyl, each of which is substituted  
with hydroxyiminomethyl or amino(hydroxyimino)(lower)-  
alkyl.

30

In the above and subsequent description of the present  
specification, suitable examples of the various definitions  
to be included within the scope of the invention are  
explained in detail in the following.

35

The term "lower" is intended to mean a group having 1 to 6 carbon atom(s), unless otherwise provided.

The "higher" is intended to mean 7 to 20 carbon atoms, unless otherwise provided.

5       The lower moiety in the terms "cyclo(lower)alkyl" and "cyclo(lower)alkyloxy" is intended to mean a group having 3 to 6 carbon atoms.

10       The lower moiety in the terms "lower alkenyl", "lower alkenyloxy" and "lower alkynyl" is intended to mean a group having 2 to 6 carbon atoms.

The term "alkoxy" may include lower alkoxy and higher alkoxy.

15       Suitable "lower alkoxy" and lower alkoxy moiety in the terms "ar(lower)alkoxy", "lower alkoxy(lower)alkylamino", "acyl(lower)alkoxy", "acyl(lower)alkoxyimino", "esterified carboxy(lower)alkoxyimino", "carboxy(lower)-alkoxyimino", "N-containing heterocycliccarbonyl(lower)-alkoxyimino", "carbamoyl(lower)alkoxyimino", "lower alkylcarbamoyl(lower)alkoxyimino" and "lower alkoxycarbonyl" may be straight or branched C<sub>1</sub>-C<sub>6</sub> alkoxy such as methoxy, ethoxy, propoxy, isopropoxy, methylpropoxy, butoxy, isobutoxy, tert-butoxy, pentyloxy, hexyloxy or the like.

20       Suitable "higher alkoxy" may be straight or branched C<sub>7</sub>-C<sub>20</sub> alkoxy such as heptyloxy, octyloxy, nonyloxy, decyloxy, undecyloxy, dodecyloxy, tridecyloxy, tetradecyloxy, pentadecyloxy, hexadecyloxy, heptadecyloxy, octadecyloxy, nonadecyloxy, eicosyloxy, methylheptyloxy, methyloctyloxy, methylnonyloxy, methyldecyloxy, ethylheptyloxy, ethyloctyloxy, ethylnonyloxy, ethyldecyloxy or the like, in which preferable one is heptyloxy.

25       Suitable "lower alkyl" and lower alkyl moiety in the terms "amino(lower)alkyl(lower)alkylamino", "lower alkylamino(lower)alkylamino", "mercapto(lower)alkyl", "lower alkylhydrazino", "lower alkylthio", "N-protected lower alkylamino(lower)alkylamino", "N-protected

35

amino(lower)alkyl(N'-lower alkyl)amino",  
 "amino(lower)alkyl(N-lower alkyl)amino", "lower  
 alkylamino(lower)alkyl(N-lower alkyl)amino, "lower  
 alkoxy(lower)alkylamino", "acyl(lower)alkylsulfinyl",  
 5 "acyl(lower)alkylsulfonyl", "lower  
 alkylamino(lower)alkylcarbamoxyloxy", "acyl(lower)alkylamino",  
 "N-protected-acyl(lower)alkylamino", "N-acyl(lower)alkyl-N-  
 lower alkylamino", "lower alkylhydrazinocarbonylamino",  
 "esterified carboxy(lower)alkylamino", "N-protected-  
 10 esterified carboxy(lower)alkylamino", "N-esterified  
 carboxy(lower)alkyl-N-lower alkylamino",  
 "carboxy(lower)alkylamino",  
 "N-protected-carboxy(lower)alkylamino",  
 "N-carboxy(lower)alkyl-N-lower alkylamino", "lower  
 15 alkylcarbamoxy", "lower alkylcarbamoxy(lower)alkylamino",  
 "lower alkylcarbamoxy(lower)alkoxyimino", "N-protected-  
 (substituted or unsubstituted N-containing heterocyclic)-  
 carbonyl(lower)alkylamino", "N-protected-carbamoxy(lower)-  
 alkylamino", "N-protected-substituted or unsubstituted lower  
 20 alkylcarbamoxy(lower)alkylamino:", "N-(substituted or  
 unsubstituted N-containing heterocyclic)carbonyl(lower)alkyl-  
 N-lower alkylamino", "N-carbamoxy(lower)alkyl-N-lower  
 alkylamino", "N-lower alkylcarbamoxy-N-lower alkylamino",  
 "lower alkylcarbamoxy(lower)alkoxyimino",  
 25 "1-hydroxy(lower)alkyl", "1-(lower alkyl)amino(lower)alkyl",  
 "mono(lower)alkylamino", "lower alkylamino(lower)alkyl",  
 "acyloxy(lower)alkyl", "halo(lower)alkyl", "lower  
 alkoxy(lower)alkyl", "protected hydroxy(lower)alkyl",  
 "hydroxy(lower)alkyl", "ar(lower)alkyl", "protected  
 30 amino(lower)alkyl", "amino(lower)alkyl",  
 "a heterocyclic(lower)alkyl", "acyl(lower)alkyl",  
 "di(lower)alkylamino", "lower alkylsulfonyl" and "lower  
 alkylamino" may be straight or branched C<sub>1</sub>-C<sub>6</sub> alkyl such as  
 methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-  
 35 butyl, pentyl, ethylpropyl, hexyl or the like.

Suitable "cyclo(lower)alkyl" and cyclo(lower)alkyl moiety in the term "cyclo(lower)alkyloxy" may be cyclo-(C<sub>3</sub>-C<sub>6</sub>)alkyl such as cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

5        Suitable "aryl", aryl moiety in the terms "aryloxy", "haloaryl", "arylsulfonyl", "acyl-substituted aryl", "(N-arylmethyl)lower alkoxy(lower)alkylbenzimidazolyl" and "(N-lower alkoxyarylmethyl)acylbenzimidazolyl" and ar moiety in the terms "ar(lower)alkyl" and "ar(lower)alkoxy" may be  
10        phenyl, naphthyl, phenyl substituted with lower alkyl [e.g. tolyl, xylyl, mesityl, cumenyl, di(tert-butyl)phenyl, etc.] and the like, in which preferable one is phenyl, tolyl or xylyl.

      Suitable "substituted aryl" may be aryl substituted with  
15        suitable substituent(s) such as acyl, substituted acyl, N-protected piperazinylsulfonyl, piperazinylsulfonyl, N-lower alkylpiperazinylsulfonyl, hydroxy(lower)alkyl, a heterocyclic(lower)alkyl, halogen, nitro, amino, lower alkylamino, a heterocyclic group [e.g. thiazolyl, oxazolyl, tetrazolyl, oxazolynyl, pyridyl, pyrimidinyl, pyrrolyl  
20        optionally substituted with lower alkyl and cyano, etc.], cyano, lower alkoxy or the like, in which preferable one for the substituent of alkoxy for R<sup>1</sup> is aryl substituted with N-lower alkylpiperazinylcarbonyl.

25        Suitable "halogen" and halo moiety in the terms "halo(lower)alkyl" and "haloaryl" may be fluorine, chlorine, bromine and iodine, in which preferable one is chlorine or bromine.

      Suitable "lower alkylamino" and lower alkylamino moiety  
30        in the terms "amino(lower)alkyl(lower)alkylamino", "lower alkylamino(lower)alkylamino", "N-protected lower alkylamino(lower)alkylamino", "N-protected amino(lower)(N'-lower alkyl)amino", "amino(lower)alkyl(N-lower alkyl)amino", "lower alkylamino(lower)alkyl(N-lower alkyl)amino", "lower  
35        alkoxy(lower)alkylamino", "lower

alkylamino(lower)alkylcarbamoxyloxy", "acyl(lower)alkylamino",  
"esterified carboxy(lower)alkylamino",  
"carboxy(lower)alkylamino",  
"N-containing heterocycliccarbonyl(lower)alkylamino",  
5 "carbamoxy(lower)alkylamino",  
"lower alkylcarbamoxy(lower)alkylamino",  
"lower alkylamino(lower)alkyl" and "lower  
alkylaminopiperidylcarbonyl" may be mono or di(lower  
alkyl)amino such as methylamino, ethylamino, propylamino,  
10 isopropylamino, butylamino, tert-butylamino, isobutylamino,  
pentylamino, hexylamino, dimethylamino, diethylamino,  
dipropylamino, dibutylamino, diisopropylamino, dipentylamino,  
dihexylamino, N-methylethylamino or the like, in which  
preferable one is methylamino, dimethylamino or diethylamino.

15 Suitable "lower alkylhydrazino" may be 2-mono or  
2,2-di(lower alkyl)hydrazino such as 2-methylhydrazino,  
2,2-dimethylhydrazino, 2-ethylhydrazino, 2,2-diethylhydrazino  
or the like, in which preferable one 2,2-dimethylhydrazino.

Suitable "1-hydroxy(lower)alkyl" may be 1-hydroxy-  
20 (C<sub>1</sub>-C<sub>6</sub>)alkyl such as hydroxymethyl, 1-hydroxyethyl,  
1-hydroxypropyl, 1-hydroxybutyl, 1-hydroxy-3-methylpropyl or  
the like, in which preferable one is hydroxymethyl or  
1-hydroxyethyl.

Suitable "1-(lower alkyl)amino(lower)alkyl" may be  
25 1-mono or di(C<sub>1</sub>-C<sub>6</sub> alkyl)amino(C<sub>1</sub>-C<sub>6</sub>)alkyl such as  
methylaminomethyl, dimethylaminomethyl, 1-methylaminoethyl,  
1-dimethylaminoethyl, ethylaminomethyl, 1-ethylaminoethyl or  
the like, in which preferable one is methylaminomethyl,  
dimethylaminomethyl, 1-methylaminoethyl or  
30 1-dimethylaminoethyl.

Suitable "lower alkylamino(lower)alkyl" may be mono or  
di(lower alkyl)amino(lower)alkyl such as methylaminomethyl,  
dimethylaminomethyl, dimethylaminoethyl or the like.

Suitable "amino(lower)alkyl(lower)alkylamino" may be  
35 aminomethylmethylamino, aminomethylethylamino,

aminoethylmethyldamino, aminoethylethylamino and the like, in which preferable one is aminoethylmethyldamino.

Suitable "lower alkylamino(lower)alkylamino" may be mono or di(lower alkyl)amino(lower)alkylamino such as  
5 methylethylamino, dimethylethylamino and the like.

Suitable "N-protected lower alkylamino(lower)alkylamino" may be N-tert-butoxycarbonyl(lower)alkylamino(lower)-alkylamino such as N-tert-butoxycarbonylmethyldaminoethylamino or the like.

10 Suitable "N-protected amino(lower)alkyl(N'-lower alkyl)amino" may be N-tert-butoxycarbonylamino(lower)alkyl-(N'-lower alkyl)amino such as N-tert-butoxycarbonylamino-ethyl(N-methyl)amino or the like.

15 Suitable "amino(lower)alkyl(N-lower alkyl)amino" may be aminoethyl(N-methyl)amino or the like.

Suitable "lower alkylamino(lower)alkyl(N-lower alkyl)-amino" may be mono or di(lower alkyl)amino(lower)alkyl(N-lower alkyl)amino such as dimethyldaminoethyl(N-methyl)amino or the like.

20 Suitable "lower alkoxy(lower)alkylamino" may be methoxyethylamino and the like.

Suitable "acyloxy(lower)alkyl" may be pivaloyloxymethyl and the like.

25 Suitable "lower alkoxy(lower)alkyl" may be methoxymethyl and the like.

"hydroxy-protective group" in protected hydroxy moiety in the term "protected hydroxy(lower)alkyl" may be common hydroxy-protective group such as substituted or unsubstituted arylmethyl (e.g. benzyl, lower alkoxybenzyl, etc.), acyl, 30 substituted silyl (e.g. tert-butyldiphenylsilyl, etc.) or the like.

Suitable "heterocyclic group" may be one containing at least one hetero atom selected from nitrogen, sulfur and oxygen atom, and may include saturated or unsaturated, 35 monocyclic or condensed heterocyclic group, and preferable

heterocyclic group may be N-containing heterocyclic group such as unsaturated 3 to 6-membered heteromonocyclic group containing 1 to 4 nitrogen atoms, for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl, pyrimidinyl, 5 pyrazinyl, pyridazinyl, triazolyl [e.g. 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.], tetrazolyl [e.g. 1H-tetrazolyl, 2H-tetrazolyl, etc.], etc.;

saturated 3 to 7-membered heteromonocyclic group containing 1 to 4 nitrogen atoms [e.g. pyrrolidinyl, imidazolidinyl, 10 piperidyl, piperazinyl, homopiperazinyl, etc.];

saturated condensed heterocyclic group containing 1 to 5 nitrogen atoms, for example, quinuclidinyl, etc.

unsaturated condensed heterocyclic group containing 1 to 5 nitrogen atoms, for example, indolyl, isoindolyl, 15 indolizinyll, benzimidazolyl, quinolyl, isoquinolyl, imidazopyridyl [e.g. imidazo[4,5-b]pyridyl, imidazo[1,2-a]pyridyl, imidazo[3,4-a]pyridyl, etc.], purinyl, indazolyl, benzotriazolyl, tetrazolopyridazinyl [e.g. tetrazolo[1,5-b]-pyridazinyl, etc.], indolinyl, tetrahydroquinolyl, 20 quinoxalinyl, 1H-indazolyl, 1H-pyrazolo[1,5-b][1,2,4]-triazolyl, quinazolinyl, etc.;

unsaturated 3 to 6-membered heteromonocyclic group containing an oxygen atom, for example, pyranyl, furyl, etc.;

saturated 3 to 6-membered heteromonocyclic group containing an oxygen atom, for example, 1H-tetrahydropyranyl, 25 tetrahydrofuranlyl, etc.;

unsaturated, 3 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms, for example, thienyl, etc.;

unsaturated 3 to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, for example, 30 oxazolyl, isoxazolyl, oxadiazolyl [e.g. 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc.], oxazolinyl [e.g. 2,5-oxazolinyl, etc.], oxazinyl [e.g. 3H,4H,5H-2,6-oxazinyl, etc.], etc.;

35 saturated 3 to 6-membered heteromonocyclic group containing 1

to 2 oxygen atoms and 1 to 3 nitrogen atoms [e.g. morpholinyl, etc.];

unsaturated condensed heterocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms [e.g. benzofurazanyl, benzoxazolyl, benzoxadiazolyl, benzoxazinyl, etc.];

unsaturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms, for example, thiazolyl, thiadiazolyl [e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, etc.], etc.;

saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms [e.g., thiazolidinyl, etc.];

unsaturated condensed heterocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms [e.g., benzothiazolyl, benzothiadiazolyl, etc.];

unsaturated condensed heterocyclic group containing 1 to 2 oxygen atoms [e.g. benzofuranyl, benzodioxolyl, etc.] and the like.

Said "heterocyclic group" includes one substituted with lower alkyl as exemplified above or oxo, and spiro-typed one substituted with C<sub>2</sub>-C<sub>6</sub> alkylene, in which preferable one is N-methylpiperazinyl, tetrazolyl, morpholinyl, pyrrolidinyl, N-methylpiperidyl, N-methylhomopiperazinyl, 1H-tetrahydropyranyl, thienyl, pyridyl, piperidyl, oxopiperidyl, pyrrolyl, oxazolyl, 2,5-oxazolinyl, 4,4-dimethyl(2,5-oxazolinyl), 1-aza-3-oxaspiro[4.4]non-1-en-2-yl, 3H,4H,5H-2,6-oxazinyl.

Suitable "condensed heterocyclic group" may be saturated or unsaturated one above-mentioned, in which preferable one is indolyl, benzimidazolyl, benzoxazolyl, benzotriazolyl, imidazopyridyl (e.g. imidazo[4,5-b]pyridyl, imidazo[1,2-a]pyridyl, imidazo[3,4-a]pyridyl, etc.), purinyl, indolinyl, tetrahydroquinolyl, quinoxalinyl, 1H-indazolyl, 1H-pyrazolo[1,5-b][1,2,4]triazolyl, quinazolinyl, 2H-1,4-benzoxazin-3-oxo-8-yl.



Suitable acyl and acyl moiety in the terms  
"acyl(lower)alkylsulfinyl", "acyl(lower)alkylsulfonyl",  
"acyloxy", "acyloxy(lower)alkyl", "acylamino",  
"acyl(lower)alkanoyloxy", "acyl(lower)alkoxyimino",  
5 "acyl(lower)alkylamino", "N-protected-acyl(lower)alkylamino",  
"N-acyl(lower)alkyl-N-lower alkylamino" and  
"acyl(lower)alkoxy" may be carboxy, esterified carboxy,  
carbamoyl, lower alkylcarbamoyl, lower alkanoyl, aroyl, a  
heterocycliccarbonyl, lower alkylsulfonyl, arylsulfonyl,  
10 sulfamoyl, lower alkylsulfamoyl and the like.

The esterified carboxy may be substituted or  
unsubstituted lower alkoxy carbonyl [e.g. methoxycarbonyl,  
ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl,  
tert-butoxycarbonyl, hexyloxycarbonyl, 2-iodoethoxycarbonyl,  
15 2,2,2-trichloroethoxycarbonyl, dimethylaminopropoxycarbonyl,  
dimethylaminoethoxycarbonyl, etc.], substituted or  
unsubstituted aryloxycarbonyl [e.g. phenoxycarbonyl,  
4-nitrophenoxycarbonyl, 2-naphthyloxycarbonyl, etc.],  
substituted or unsubstituted ar(lower)alkoxy carbonyl [e.g.  
20 benzyloxycarbonyl, phenethyloxycarbonyl,  
benzhydryloxycarbonyl, 4-nitrobenzyloxycarbonyl,  
3-methoxy-4-nitrobenzyloxycarbonyl, etc.], N-containing  
heterocyclicoxycarbonyl [e.g. N-methylpiperidyloxycarbonyl,  
etc.] and the like.

25 The lower alkylcarbamoyl may be mono or di(lower alkyl)-  
carbamoyl such as methylcarbamoyl, ethylcarbamoyl,  
propylcarbamoyl, dimethylcarbamoyl, diethylcarbamoyl,  
N-methyl-N-ethylcarbamoyl or the like.

The lower alkanoyl may be substituted or unsubstituted  
30 C<sub>1</sub>-C<sub>6</sub> alkanoyl such as formyl, acetyl, propionyl, butyryl,  
isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl,  
trifluoroacetyl or the like, in which preferable one is  
formyl or acetyl.

The aroyl may be benzoyl, naphthoyl, toluoyl, di(tert-  
35 butyl)benzoyl and the like, in which preferable one is

benzoyl.

The heterocyclic moiety in the terms "a heterocyclic-carbonyl", "heterocyclicoxycarbonylamino", "heterocycliccarbamoyl" and "heterocyclicsulfonyl" may be one  
5 mentioned above as a heterocyclic group.

Preferred "a heterocycliccarbonyl" may be N-containing heterocycliccarbonyl.

The "N-containing heterocycliccarbonyl" may be one containing at least one nitrogen atom in heterocyclic group  
10 mentioned above, in which preferable one is N-(lower alkyl)-piperazinylcarbonyl (e.g. N-methylpiperazinylcarbonyl, etc.), N-(lower alkyl)homopiperazinylcarbonyl (e.g. N-methylhomopiperazinylcarbonyl, etc.), piperazinylcarbonyl, pyrrolidinylcarbonyl, piperidylcarbonyl, morpholinocarbonyl,  
15 lower alkylpiperidylcarbonyl (e.g. methylpiperidylcarbonyl, etc.) or oxopiperidylcarbonyl.

Suitable "substituted acyl" may be carbamoyl substituted with amino, a heterocyclic group [e.g. N-(lower alkyl)piperazinyl, pyridyl, etc.], lower alkylsulfonyl or  
20 arylsulfonyl, substituted lower alkylcarbamoyl [e.g. N-lower alkylamino-N-lower alkylcarbamoyl, pyridyl(lower)alkylcarbamoyl, morpholino(lower)alkylcarbamoyl, bis(hydroxy(lower)alkyl)carbamoyl,  
25 hydroxy(lower)alkylcarbamoyl, carbamoyl(lower)alkylcarbamoyl, lower alkylamino(lower)alkylcarbamoyl, N-lower alkyl-N-lower alkylcarbamoyl, etc.], substituted N-containing heterocycliccarbonyl [e.g. trifluoroacetyl-piperazinylcarbonyl,  
30 pyridylpiperazinylcarbonyl, hydroxypiperidylcarbonyl, dimethylaminopiperidylcarbonyl, diethylaminopiperidylcarbonyl, carbamoylpyrrolidinylcarbonyl, dimethylaminopiperazinylcarbonyl, hydroxyethoxyethylpiperazinylcarbonyl,  
35 pyrrolidinylcarbonylmethylpiperazinylcarbonyl, etc.],

N-protected-N-containing heterocycliccarbonyl [e.g. N-t-butoxycarbonylpiperidylcarbonyl, N-t-butoxycarbonylpiperazinylcarbonyl, etc.], N-protected amino(lower)alkanoyl, amino(lower)alkanoyl, benzyloxybenzoyl, and the like.

"N-Protective group" in "protected amino" may be common N-protective group such as substituted or unsubstituted lower alkanoyl [e.g. formyl, acetyl, propionyl, trifluoroacetyl, etc.], phthaloyl, lower alkoxycarbonyl [e.g. tert-butoxycarbonyl, tert-amylloxycarbonyl, etc.], substituted or unsubstituted aralkyloxycarbonyl [e.g. benzyloxycarbonyl, p-nitrobenzyloxycarbonyl, etc.], 9-fluorenylmethoxycarbonyl, substituted or unsubstituted arenesulfonyl [e.g. benzenesulfonyl, tosyl, etc.], nitrophenylsulfenyl, aralkyl [e.g. trityl, benzyl, etc.] or the like, in which preferable one is phthaloyl, tert-butoxycarbonyl or 9-fluorenylmethoxycarbonyl.

"N-protective group" in "N-protected guanidino" may be common N-protective group such as lower alkoxycarbonyl [e.g. tert-butoxycarbonyl, etc.] or the like.

Suitable "acid residue" may be halogen [e.g. fluoro, chloro, bromo, iodo], arenesulfonyloxy [e.g. benzenesulfonyloxy, tosyloxy, etc.], alkanesulfonyloxy [e.g. mesyloxy, ethanesulfonyloxy, etc.], and the like, in which preferable one is halogen.

Suitable "lower alkylsulfonyl" may be (C<sub>1</sub>-C<sub>6</sub>)-alkylsulfonyl such as methylsulfonyl, ethylsulfonyl, propylsulfonyl or the like, in which preferable one is methylsulfonyl.

Suitable "arylsulfonyl" may be phenylsulfonyl, tolylsulfonyl and the like.

The substituent(s) on aryl for R<sup>1</sup> or a condensed heterocyclic group for Y, and the substituent(s) on lower alkyl as substituent of a condensed heterocyclic group for Y may be plural and in such case the substituents may be the

same or different.

Preferred "aryl" for  $R^1$  may be phenyl or phenyl substituted with lower alkyl.

Preferred "a heterocyclic group" as substituent of aryl  
5 for  $R^1$  may be piperidino, N-lower alkylpiperazinyl [e.g. N-methylpiperazinyl, etc.], morpholino, 4,4-dimethyl(2,5-oxazolinyl), pyrrolyl, 2,5-oxazolyl, 2,5-oxazolinyl, 3H,4H,5H-2,6-oxazinyl or 1-aza-3-oxaspiro[4.4]non-1-en-2-yl.

Preferred "a heterocyclic group" in a heterocyclic-  
10 (lower)alkyl as substituent of a condensed heterocyclic group for Y may be pyridyl, N-lower alkylpiperazinyl [e.g. N-methylpiperazinyl, etc.], morpholino, imidazolyl, pyrrolidinyl.

Preferred "substituted-heterocyclic group" in  
15 substituted heterocyclic(lower)alkyl as substituent of a condensed heterocyclic group for Y may be substituted-piperidyl such as lower alkylaminopiperidyl including mono or di(lower alkyl)aminopiperidyl [e.g. dimethylaminopiperidyl, etc.] or the like.

Preferred compound (I) is one having tolyl which is  
20 substituted with lower alkoxy substituted with N-(lower alkyl)piperazinylcarbonyl for  $R^1$ , lower alkyl for  $R^2$ , lower alkoxy for  $R^3$ , NH for A and  $\overset{\text{O}}{\underset{\text{||}}{\text{C}}}$  for E, or a single bond for A

25  $\overset{\text{O}}{\underset{\text{||}}{\text{C}}}\text{NH-}$  for E,  $\text{-CH=CH-}$  for X and benzimidazolyl which is substituted with lower alkyl optionally substituted with hydroxy, amino or N-lower alkyl piperazinyl for Y.

Suitable pharmaceutically acceptable salts of the object  
30 compound (I) are conventional non-toxic salts and include an acid addition salt such as an inorganic acid addition salt [e.g. hydrochloride, hydrobromide, sulfate, phosphate, etc.], an organic acid addition salt [e.g. formate, acetate, trifluoroacetate, maleate, tartrate, methanesulfonate,  
35 benzenesulfonate, toluenesulfonate, etc.], a metal salt such

as an alkali metal salt [e.g. sodium salt, potassium salt, etc.] and an alkaline earth metal salt [e.g. calcium salt, magnesium salt, etc.] and the like.

- 5           The processes for preparing the object compound (I) are explained in detail in the following.

Process 1

- 10           The object compound (Ia) or its salt can be prepared by reacting a compound (II) or its salt with a compound (III) or its reactive derivative at the carboxy group or the sulfo group, or a salt thereof.

Suitable salts of the compounds (Ia) and (II) may be the same as those exemplified for the compound (I).

- 15           Suitable salts of the compound (III) and its reactive derivative at the carboxy group or the sulfo group may be base salts as exemplified for the compound (I).

- 20           Suitable reactive derivative at the carboxy group or the sulfo group of the compound (III) may include an acid halide, an acid anhydride containing intramolecular, intermolecular and a mixed ones, an activated amide, an activated ester, and the like. Suitable examples of the reactive derivatives may be an acid chloride; an acid azide; a mixed acid anhydride with an acid such as substituted phosphoric acid [e.g. dialkylphosphoric acid, phenylphosphoric acid, diphenylphosphoric acid, dibenzylphosphoric acid, halogenated phosphoric acid, etc.], dialkylphosphorous acid, sulfurous acid, thiosulfuric acid, sulfuric acid, sulfonic acid [e.g. methanesulfonic acid, etc.], aliphatic carboxylic acid [e.g. acetic acid, propionic acid, butyric acid, isobutyric acid, pivalic acid, pentanoic acid, isopentanoic acid, 2-ethylbutyric acid, trichloroacetic acid, etc.] or aromatic carboxylic acid [e.g. benzoic acid, etc.]; a symmetrical acid anhydride; an activated amide with imidazole, 4-substituted imidazole, dimethylpyrazole, triazole or tetrazole; or
- 35

an activated ester [e.g. ethyl ester, cyanomethyl ester, methoxymethyl ester, dimethyliminomethyl  $\{(\text{CH}_3)_2\text{N}^+=\text{CH}-\}$  ester, intramolecular trifluoromethyl-substituted iminomethyl ester, vinyl ester, propargyl ester, p-nitrophenyl ester, 2,4-dinitrophenyl ester, trichlorophenyl ester, pentachlorophenyl ester, mesylphenyl ester, phenylazophenyl ester, phenyl thioester, p-nitrophenyl thioester, p-cresyl thioester, carboxymethyl thioester, pyranyl ester, pyridyl ester, piperidyl ester, 8-quinolyl thioester, etc.] or an ester with an N-hydroxy compound [e.g. N,N-dimethylhydroxylamine, 1-hydroxy-2-(1H)-pyridone, N-hydroxysuccinimide, N-hydroxyphthalimide, 1-hydroxy-1H-benzotriazole, etc.], and the like. These reactive derivatives can optionally be selected from them according to the kind of the compound (III) to be used.

The reaction is usually carried out in a conventional solvent such as water, alcohol [e.g. methanol, ethanol, etc.], acetone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, pyridine or any other organic solvent which does not adversely influence the reaction. These conventional solvents may also be used in a mixture with water.

In this reaction, when the compound (III) is used in a free acid form or its salt form, the reaction is preferably carried out in the presence of a conventional condensing agent such as N,N'-dicyclohexylcarbodiimide; N-cyclohexyl-N'-morpholinoethylcarbodiimide; N-cyclohexyl-N'-(4-diethylaminocyclohexyl)carbodiimide; N,N'-diethylcarbodiimide, N,N'-diisopropylcarbodiimide; N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide; N,N'-carbonylbis-(2-methylimidazole); pentamethyleneketene-N-cyclohexylimine; diphenylketene-N-cyclohexylimine; ethoxyacetylene; 1-alkoxy-1-chloroethylene; trialkyl phosphite; ethyl

polyphosphate; isopropyl polyphosphate; phosphorus  
oxychloride (phosphoryl chloride); phosphorus trichloride;  
diphenylphosphoryl azide; diphenyl chlorophosphate;  
diphenylphosphinic chloride; thionyl chloride; oxalyl  
5 chloride; lower alkyl haloformate [e.g. ethyl chloroformate,  
isopropyl chloroformate, etc.]; triphenylphosphine;  
2-ethyl-7-hydroxybenzisoxazolium salt;  
2-ethyl-5-(m-sulfophenyl)isoxazolium hydroxide intramolecular  
salt; 1-(p-chlorobenzenesulfonyloxy)-6-chloro-1H-  
10 benzotriazole; so-called Vilsmeier reagent prepared by the  
reaction of N,N-dimethylformamide with thionyl chloride,  
phosgene, trichloromethyl chloroformate, phosphorus  
oxychloride, etc.; or the like.

The reaction may also be carried out in the presence of  
15 an inorganic or organic base such as an alkali metal  
bicarbonate, tri(lower)alkylamine, pyridine,  
4-dimethylaminopyridine, N-(lower)alkylmorpholine,  
N,N-di(lower)alkylbenzylamine, or the like.

The reaction temperature is not critical, and the  
20 reaction is usually carried out under cooling to heating.

In this reaction, in case that the compound (II) having  
aryl substituted with phthalimido for  $R^1$ , the compound (Ia)  
having aryl substituted with amino may be obtained according  
to reaction condition.

25 This case is included within the scope of this reaction.

### Process 2

The object compound (Ic) or its salt can be prepared by  
reacting a compound (Ib) or its salt with a compound (IV) in  
30 the presence of a base.

Suitable salts of the compounds (Ib) and (Ic) may be the  
same as those exemplified for the compound (I).

Suitable base may be an alkali metal (e.g. sodium,  
potassium, etc.), an alkali metal hydride (e.g. sodium  
35 hydride), an alkali metal alkoxide (e.g. potassium tert-

butoxide, etc.) and the like.

The reaction is carried out in a solvent such as N,N-dimethylformamide, tetrahydrofuran, dioxane, a mixture thereof or any other solvent which does not adversely influence the reaction.

The reaction temperature is not critical and the reaction is usually carried out under cooling to warming.

### Process 3

The object compound (Ie) or its salt can be prepared by subjecting a compound (Id) or its salt to reduction.

Suitable salts of the compounds (Id) and (Ie) may be the same as those exemplified for the compound (I).

The reduction may include chemical reduction and catalytic reduction, which are carried out in a conventional manner.

Suitable reducing agents to be used in chemical reduction are a metal [e.g. tin, zinc, iron, nickel, etc.], a combination of such metal and/or metallic compound [e.g. nickel chloride, chromium chloride, chromium acetate, etc.] and an organic or inorganic acid [e.g. formic acid, acetic acid, propionic acid, trifluoroacetic acid, p-toluenesulfonic acid, hydrochloric acid, hydrobromic acid, etc.], a combination of such metal and/or metallic compound and base [e.g. ammonia, ammonium chloride, sodium hydroxide, etc.], a metal hydride compound such as aluminum hydride compound [e.g. lithium aluminum hydride, sodium aluminum hydride, aluminum hydride, lithium trimethoxyaluminum hydride, lithium tri-t-butoxyaluminum hydride, etc.], borohydride compound [e.g. sodium borohydride, lithium borohydride, sodium cyanoborohydride, tetramethylammonium borohydride, borane, diborane, etc.], a phosphorus compound [e.g. phosphorus trichloride, phosphorus tribromide, triphenylphosphine, triethylphosphine, etc.] and the like.

Suitable catalysts to be used in catalytic reduction are



conventional ones such as platinum catalysts [e.g. platinum plate, spongy platinum, platinum black, colloidal platinum, platinum oxide, platinum wire, etc.], palladium catalyst [e.g. spongy palladium, palladium black, palladium oxide, palladium on carbon, colloidal palladium, palladium on barium sulfate, palladium on barium carbonate, etc.], nickel catalyst [e.g. reduced nickel, nickel oxide, Raney nickel, etc.], cobalt catalyst [e.g. reduced cobalt, Raney cobalt, etc.], iron catalyst [e.g. reduced iron, Raney iron, etc.], copper catalyst [e.g. reduced copper, Raney copper, Ullman copper, etc.], or the like.

The reduction is usually carried out in a solvent. A suitable solvent to be used may be water, an alcohol [e.g. methanol, ethanol, propanol, etc.], acetonitrile or any other conventional organic solvent such as diethyl ether, dioxane, tetrahydrofuran, etc. or a mixture thereof.

The reaction temperature is not critical, and the reaction is preferably carried out under cooling to heating.

#### 20 Process 4

The object compound (If) or its salt can be prepared by reacting a compound (Ie) or its salt with aroyl halide, cyano(lower)alkylcarboxylic acid, mercapto(lower)alkylcarboxylic acid, lower alkyl lactone, 1,1-dihalo-1,1-diphenoxymethane, diphenyl N-sulfamoylcarbonimidate, diphenyl N-cyanocarbonimidate, dicyandiamide, 1,1'-thiocarbonyl-diimidazole, cyanogen bromide, lower alkoxycarbonyl isothiocyanate, tri(lower)alkyl orthoformate, tetra(lower)alkyl orthocarbonate, lower alkylcarboxylic acid, halo(lower)alkylcarboxylic acid, protected amino(lower)-alkylcarbonyl halide or a heterocyclic(lower)alkylcarbonyl halide.

Suitable salts of the compounds (Ie) and (If) may be the same as those exemplified for the compound (I).

35 The reaction is carried out in no solvent or a solvent

such as water, hydrochloric acid, tetrahydrofuran, ethyl acetate, acetonitrile, benzene, acetic acid, dichloromethane, pyridine, an alcohol (e.g. methanol, ethanol, isopropanol, etc.), a mixture thereof or any other solvent which does not adversely influence the reaction.

The reaction is also preferably carried out in the presence of base (e.g. sodium carbonate, etc.) or a conventional condensing agent such as N,N'-dicyclohexylcarbodiimide, p-toluenesulfonic acid, or the like.

The reaction temperature of this reaction is not critical and the reaction is usually carried out under cooling to heating.

#### Process 5

The object compound (Ig) or its salt can be prepared by reacting a compound (Ie) or its salt with glyoxal and sodium hydrogen sulfite, or sodium nitrite.

Suitable salts of the compounds (Ie) and (Ig) may be the same as those exemplified for the compound (I).

The reaction is usually carried out in a solvent such as water, acetic acid, an alcohol (e.g. methanol, ethanol, etc.), a mixture thereof or any other solvent which does not adversely influence the reaction.

The reaction temperature of this reaction is not critical and the reaction is usually carried out under cooling to heating.

#### Process 6

The object compound (Ih) or its salt can be prepared by reacting a compound (Ib) or its salt with an acylating agent.

Suitable salts of the compounds (Ib) and (Ih) may be the same as those exemplified for the compound (I).

The acylating agent may include an organic acid represented by the formula :  $R^7-OH$ , in which  $R^7$  is acyl as illustrated above, or its reactive derivative.

The suitable reactive derivative of organic acid may be a conventional one such as an acid halide [e.g. acid chloride, acid bromide, etc.], an acid azide, an acid anhydride containing intramolecular and intermolecular ones,  
5 an activated amide, an activated ester or the like.

When free acid is used as an acylating agent, the acylation reaction may preferably be conducted in the presence of a conventional condensing agent such as N,N'-dicyclohexylcarbodiimide or the like.

10 The reaction is usually carried out in a conventional solvent such as water, pyridine, acetone, dioxane, chloroform, methylene chloride, acetonitrile, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, pyridine or any other organic solvent which does  
15 not adversely influence the reaction, or a mixture thereof.

The reaction is also preferably carried out in the presence of a conventional base such as triethylamine, pyridine, N,N-dimethylaminopyridine, sodium hydroxide or the like.

20 The reaction temperature is not critical, and the reaction can be carried out under cooling to heating.

#### Process 7

The object compound (Ij) or its salt can be prepared by subjecting a compound (Ii) or its salt to elimination  
25 reaction of the N-substituent group.

Suitable salts of the compounds (Ii) and (Ij) may be the same as those exemplified for the compound (I).

The reaction is carried out in accordance with a conventional method such as hydrolysis, reduction or the like.

30 In case that the N-substituent group is acyl, acyloxymethyl or lower alkoxyarylmethyl, the reaction is preferably carried out in accordance with hydrolysis, and in case that the N-substituent is arylmethyl, the reaction is preferably carried out in accordance with reduction.

35 The hydrolysis is preferably carried out in the presence

of a base or an acid including Lewis acid.

Suitable base may include an inorganic base and an organic base such as an alkali metal [e.g. sodium, potassium, etc.], an alkaline earth metal [e.g. magnesium, calcium, etc.], the hydroxide or carbonate or bicarbonate or lower alkoxide thereof, hydrazine, alkylamine [e.g. methylamine, trimethylamine, triethylamine, etc.], picoline, 1,5-diazabicyclo[4.3.0]non-5-ene, 1,4-diazabicyclo[2.2.2]octane, 1,8-diazabicyclo[5.4.0]undec-7-ene, or the like.

Suitable acid may include an organic acid [e.g. formic acid, acetic acid, propionic acid, trichloroacetic acid, trifluoroacetic acid, etc.], an inorganic acid [e.g. hydrochloric acid, hydrobromic acid, sulfuric acid, hydrogen chloride, hydrogen bromide, hydrogen fluoride, etc.] and an acid addition salt compound [e.g. pyridine hydrochloride, etc.].

The elimination using trihaloacetic acid [e.g. trichloroacetic acid, trifluoroacetic acid, etc.] or the like is preferably carried out in the presence of cation trapping agents [e.g. anisole, phenol, etc.].

The reaction is usually carried out in a solvent such as water, an alcohol [e.g. methanol, ethanol, etc.], methylene chloride, chloroform, tetrachloromethane, tetrahydrofuran, a mixture thereof or any other solvent which does not adversely influence the reaction. A liquid base or acid can be also used as the solvent. The reaction temperature is not critical and the reaction is usually carried out under cooling to heating.

The reduction method applicable for the elimination reaction may include chemical reduction and catalytic reduction.

Suitable reducing agents to be used in chemical reduction are a combination of metal [e.g. tin, zinc, iron, etc.] or metallic compound [e.g. chromium chloride, chromium

acetate, etc.] and an organic or inorganic acid [e.g. formic acid, acetic acid, propionic acid, trifluoroacetic acid, p-toluenesulfonic acid, hydrochloric acid, hydrobromic acid, etc.].

5           Suitable catalysts to be used in catalytic reduction are conventional ones such as platinum catalysts [e.g. platinum plate, spongy platinum, platinum black, colloidal platinum, platinum oxide, platinum wire, etc.], palladium catalysts [e.g. spongy palladium, palladium black, palladium oxide, 10 palladium on carbon, colloidal palladium, palladium on barium sulfate, palladium on barium carbonate, etc.], nickel catalysts [e.g. reduced nickel, nickel oxide, Raney nickel, etc.], cobalt catalysts [e.g. reduced cobalt, Raney cobalt, etc.], iron catalysts [e.g. reduced iron, Raney iron, etc.], 15 copper catalysts [e.g. reduced copper, Raney copper, Ullman copper, etc.] and the like.

          In case that the N-substituent group is benzyl, the reduction is preferably carried out in the presence of a combination of palladium catalysts [e.g. palladium black, 20 palladium on carbon, etc.] and formic acid or its salt [e.g. ammonium formate, etc.].

          The reduction is usually carried out in a conventional solvent which does not adversely influence the reaction such as water, methanol, ethanol, propanol, N,N-dimethylformamide, 25 or a mixture thereof. Additionally, in case that the above-mentioned acids to be used in chemical reduction are in liquid, they can also be used as a solvent. Further, a suitable solvent to be used in catalytic reduction may be the above-mentioned solvent, and other conventional solvent such as diethyl ether, dioxane, tetrahydrofuran, etc. or a mixture 30 thereof.

          The reaction temperature of this reduction is not critical and the reaction is usually carried out under cooling to heating.

In this reaction, in case that the compound (Ii) having (N-lower alkoxy carbonyl)phthalimido(lower)alkylindolyl, (N-lower alkoxy carbonyl)lower alkylamino(lower)alkylamino-(N-lower alkoxy carbonyl)benzimidazolyl or N-lower alkoxy carbonylamino(lower)alkyl(N-lower alkyl)amino(N-lower alkoxy carbonyl)benzimidazolyl for Yh, the compound (Ij) having amino(lower)alkylindolyl, lower alkylamino(lower)-alkylaminobenzimidazolyl or amino(lower)alkyl(N-lower)-alkylaminobenzimidazolyl for Yi may be obtained according to reaction condition. This case is included within the scope of this reaction.

#### Process 8

The object compound (Ii) or its salt can be prepared by subjecting a compound (Ik) or its salt to elimination reaction of the N-protective group.

Suitable salts of the compounds (Ik) and (Ii) may be the same as those exemplified for the compound (I).

This reaction can be carried out in substantially the same manner as Process 7, and therefore the reaction mode and reaction condition (e.g. solvent, reaction temperature, etc.) of this reaction are to be referred to those as explained in Process 7.

#### Process 9

The object compound (In) or its salt can be prepared by subjecting a compound (Im) or its salt to deesterification reaction.

Suitable salts of the compounds (Im) and (In) may be the same as those exemplified for the compound (I).

The reaction is carried out in accordance with a conventional method such as hydrolysis, reduction or the like.

The hydrolysis is preferably carried out in the presence of a base or an acid including Lewis acid. Suitable base may

include an inorganic base and an organic base such as an alkali metal [e.g. lithium, sodium, potassium, etc.], an alkaline earth metal [e.g. magnesium, calcium, etc.], the hydroxide or carbonate or bicarbonate thereof, trialkylamine  
5 [e.g. trimethylamine, triethylamine, etc.], picoline, 1,5-diazabicyclo[4.3.0]non-5-ene, 1,4-diazabicyclo[2.2.2]-octane, 1,8-diazabicyclo[5.4.0]undec-7-ene, or the like. Suitable acid may include an organic acid [e.g. formic acid, acetic acid, propionic acid, trichloroacetic acid,  
10 trifluoroacetic acid, etc.], an inorganic acid [e.g. hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, etc.] and Lewis acid [e.g. boron tribromide, etc.].

The reaction is usually carried out in a solvent such as  
15 water, an alcohol [e.g. methanol, ethanol, etc.], xylene, diethylene glycol monomethyl ether, methylene chloride, tetrahydrofuran, a mixture thereof or any other solvent which does not adversely influence the reaction. A liquid base or acid can be also used as the solvent.

20 The reaction temperature is not critical and the reaction is usually carried out under cooling to warming.

The reduction can be applied preferably for elimination of the ester moiety such as 4-nitrobenzyl, 2-iodoethyl, 2,2,2-trichloroethyl, or the like. The reduction method  
25 applicable for the elimination reaction may include chemical reduction and catalytic reduction.

Suitable reducing agents to be used in chemical reduction are a combination of metal [e.g. tin, zinc, iron, palladium back, etc.] or metallic compound [e.g. chromium  
30 chloride, chromium acetate, etc.] and an organic or inorganic acid [e.g. formic acid, acetic acid, propionic acid, trifluoroacetic acid, carbamic acid, p-toluenesulfonic acid, hydrochloric acid, hydrobromic acid, etc.].

Suitable catalysts to be used in catalytic reduction are  
35 conventional ones such as platinum catalysts [e.g. platinum

plate, spongy platinum, platinum black, colloidal platinum, platinum oxide, platinum wire, etc.), palladium catalyst [e.g. spongy palladium, palladium black, palladium oxide, palladium hydroxide, palladium on carbon, colloidal  
5 palladium, palladium on barium sulfate, palladium on barium carbonate, etc.), nickel catalyst [e.g. reduced nickel, nickel oxide, Raney nickel, etc.), cobalt catalyst [e.g. reduced cobalt, Raney cobalt, etc.), iron catalyst [e.g. reduced iron, Raney iron, etc.), copper catalyst [e.g.  
10 reduced copper, Raney copper, Ullman copper, etc.) or the like.

The reduction is usually carried out in a conventional solvent which does not adversely influence the reaction such as water, an alcohol [e.g. methanol, ethanol, propanol,  
15 etc.), N,N-dimethylformamide, or a mixture thereof. Additionally, in case that the above-mentioned acids to be used in chemical reduction are in liquid, they can also be used as a solvent. Further, a suitable solvent to be used in catalytic reduction may be the above-mentioned solvent, and  
20 other conventional solvent such as diethyl ether, dioxane, tetrahydrofuran, etc., or a mixture thereof.

The reaction temperature of this reduction is not critical and the reaction is usually carried out under cooling to warming.

25

#### Process 10

The object compound (Io) or its salt can be prepared by reacting a compound (In) or its reactive derivative at the carboxy group or a salt thereof with an amine or its salt.

30 Suitable salt of amine may be an acid addition salt as exemplified for the compound (I).

Suitable salts of the compounds (In) and (Io) and its reactive derivative at the carboxy group may be the same as those exemplified for the compound (I).

35 Suitable "amine" may be ammonia, substituted or



unsubstituted lower alkylamine, substituted or unsubstituted N-containing heterocyclic compound and the like.

The substituted or unsubstituted lower alkylamine may be mono or di(lower)alkylamine (e.g. methylamine, ethylamine, propylamine, isopropylamine, butylamine, isobutylamine, pentylamine, hexylamine, dimethylamine, diethylamine, dipropylamine, dibutylamine, di-isopropylamine, dipentylamine, dihexylamine, etc.), pyridyl(lower)alkylamine, (e.g. pyridylmethylamine, etc.), lower alkylamino(lower)alkylamine (e.g. N-dimethylaminoethylamine, N-dimethylaminopropylamine, N-diethylaminoethyl-N-methylamine, etc.), morpholino(lower)alkylamine (e.g. morpholinoethylamine, etc.) or the like.

The substituted or unsubstituted N-containing heterocyclic compound may be a heterocyclic group substituted with amino (e.g. aminopyridine, N-methyl-N'-aminopiperazine, etc.), saturated 5 or 6-membered N-, or N- and S-, or N- and O-containing heterocyclic compound such as pyrrolidine, imidazolidine, piperidine, piperidone, piperazine, lower alkylaminopiperidine (e.g. dimethylaminopiperidine, etc.), N-(lower)alkylhomopiperazine (e.g. N-methylhomopiperazine, etc.), N-(lower)alkylpiperazine (e.g. N-methylpiperazine, N-ethylpiperazine, etc.), morpholine, thiomorpholine, N-pyridylpiperazine, N-hydroxy(lower)alkoxy(lower)-alkylpiperazine (e.g. N-hydroxyethoxyethylpiperazine, etc.), N-pyrrolidinylcarbonyl(lower)alkylpiperazine (e.g. N-pyrrolidinylcarbonylmethylpiperazine, etc.), or the like, in which preferable one is N-methylpiperazine.

This reaction can be carried out in substantially the same manner as Process 1, and therefore the reaction mode and reaction condition (e.g. solvent, reaction temperature, etc.) of this reaction are to be referred to those as explained in Process 1.

Process 11

The object compound (Iq) or its salt can be prepared by subjecting a compound (Ip) or its salt to elimination reaction of methyl or the hydroxy-protective group.

5        Suitable salts of the compounds (Ip) can (Iq) may be the same as those exemplified for the compound (I).

10        This reaction can be carried out in substantially the same manner as Process 7, and therefore the reaction mode and reaction condition (e.g. solvent, reaction temperature, etc.) of this reaction are to be referred to those as explained in Process 7.

In case that the hydroxy-protective group is tert-butyldiphenylsilyl, the reaction is preferably carried out in the presence of tetrabutylammonium fluoride.

15        Process 12

The object compound (Is) or its salt can be prepared by reacting a compound (Ir) or its salt with an acylating agent.

Suitable salts of the compounds (Ir) and (Is) may be the same as those exemplified for the compound (I).

20        This reaction can be carried out in substantially the same manner as Process 6, and therefore the reaction mode and reaction condition (e.g. solvent, reaction temperature, etc.) of this reaction are to be referred to those as explained in Process 6.

25

Process 13

The object compound (It) or its salt can be prepared by reacting a compound (Ib) or its salt with N-lower alkylmethylenammonium halide.

30        Suitable salts of the compounds (Ib) and (It) may be the same as those exemplified for the compound (I).

35        Suitable N-lower alkylmethylenammonium halide may be N-mono or di(lower alkyl)methylenammonium halide such as N-methylmethylenammonium chloride, N,N-dimethylmethylenammonium chloride or the like, in which preferable one is

N,N-dimethylmethyleammonium chloride.

The reaction is usually carried out in a conventional solvent which does not adversely influence the reaction such as chloroform, methylene chloride or the like.

5        The reaction temperature of this reaction is not critical and the reaction is usually carried out under cooling to heating.

#### Process 14

10        The object compound (Iv) or its salt can be prepared by subjecting a compound (Iu) or its salt to oxidation reaction.

Suitable salts of the compounds (Iu) and (Iv) may be the same as those exemplified for the compound (I).

15        Suitable oxidizing agent used in this reaction may be manganese dioxide, dimethyl sulfoxide, a mixture of dimethyl sulfoxide and oxalyl chloride or dimethyl sulfoxide and sulfur trioxide pyridine complex, and the like.

20        The reaction is usually carried out in a conventional solvent such as pentane, hexane, benzene, diethyl ether, dimethoxyethane, acetone, chloroform, dichloromethane or any other solvent which does not adversely influence the reaction.

Additionally in case that the above-mentioned oxidizing agent is liquid, it can be used as a solvent.

25        In this reaction, in case that dimethyl sulfoxide or a mixture of dimethyl sulfoxide and oxalyl chloride or dimethyl sulfoxide and sulfur trioxide pyridine complex is used as an oxidizing agent, the reaction is preferably carried out in the presence of alkali metal iodide (e.g. sodium iodide, etc.) and alkali metal carbonate (e.g. sodium carbonate) or  
30        tri(lower)alkylamine (e.g. triethylamine, etc.).

The reaction temperature is not critical, and the reaction is usually carried out under cooling to heating.

#### 35        Process 15

The object compound (Ix) or its salt can be prepared by subjecting a compound (Iw) or its salt to deesterification reaction.

5        Suitable salts of the compounds (Iw) and (Ix) may be the same as those exemplified for the compound (I).

      This reaction can be carried out in substantially the same manner as Process 9, and therefore the reaction mode and reaction condition (e.g. solvent, reaction temperature, etc.) of this reaction are to be referred to those as explained in  
10    Process 9.

#### Process 16

      The object compound (Iz) or its salt can be prepared by subjecting a compound (Iy) or its salt to elimination  
15    reaction of methyl substituted with aryl or substituted aryl.

      Suitable salts of the compounds (Iy) and (Iz) may be the same as those exemplified for the compound (I).

      This reaction can be carried out in substantially the same manner as Process 11, and therefore the reaction mode  
20    and reaction condition (e.g. solvent, reaction temperature, etc.) of this reaction are to be referred to those as explained in Process 11.

#### Process 17

25        The object compound (I-1) or its salt can be prepared by reacting a compound (Ix) or its reactive derivative at the carboxy group or a salt thereof with an amine or its salt.

      Suitable salts of the compounds (Ix) and (I-1) may be the same as those exemplified for the compound (I).

30        Suitable salts of amine may be an acid addition salt as exemplified for the compound (I).

      Suitable "amine" may be N-protected piperazine, oxopiperidine, lower alkylamine (e.g. dimethylamine, etc.), ammonia, lower alkylaminoamine (e.g. N,N-dimethylhydrazine,  
35    etc.), lower alkylamino(lower)alkyl(N-lower alkyl)amine (e.g.

dimethylaminoethyl (N-methyl) amine and the like.

This reaction can be carried out in substantially the same manner as Process 1, and therefore the reaction mode and reaction condition (e.g. solvent, reaction temperature, etc.) of this reaction are to be referred to those explained in Process 1.

#### Process 18

The object compound (I-3) or its salt can be prepared by reacting a compound (I-2) or its salt with a reducing agent.

Suitable salts of the compounds (I-2) and (I-3) may be the same as those exemplified for the compound (I).

Suitable reducing agent may be alkali metal borohydride (e.g. sodium borohydride, etc.), and the like.

The reaction is carried out in a solvent such as an alcohol (e.g. methanol, ethanol, etc.), tetrahydrofuran, or the like.

The reaction temperature is not critical and the reaction is usually carried out under cooling to warming.

#### Process 19

The object compound (I-4) or its salt can be prepared by reacting a compound (Iz) or its salt with an acylating agent.

Suitable salts of the compounds (Iz) and (I-4) may be the same as those exemplified for the compound (I).

This reaction can be carried out in substantially the same manner as Process 6, and therefore the reaction mode and reaction condition (e.g. solvent, reaction temperature, etc.) of this reaction are to be referred to those as explained in Process 6.

#### Process 20

The object compound (I-5) or its salt can be prepared by reacting a compound (Iz) or its salt with a compound (V).

Suitable salts of the compounds (Iz) and (I-5) may be

the same as those exemplified for the compound (I).

When the compound (V) having halogen for  $Z^2$  is used in this reaction, the reaction is preferably carried out in the presence of a base such as an alkali metal (e.g. sodium, potassium, etc.), an alkaline earth metal (e.g. magnesium, calcium, etc.), the hydride or hydroxide or carbonate or bicarbonate thereof.

The reaction is usually carried out in a conventional solvent which does not adversely influence the reaction such as water, dioxane, alcohol (e.g. methanol, ethanol, etc.), acetonitrile, tetrahydrofuran, acetic acid, N,N-dimethylformamide, or a mixture thereof.

The reaction temperature is not critical and the reaction can be carried out under cooling to heating.

#### Process 21

The object compound (I-6) or its salt can be prepared by subjecting a compound (I-5) or its salt to elimination reaction of the N-protective group.

Suitable salts of the compounds (I-5) and (I-6) may be the same as those exemplified for the compound (I).

This reaction can be carried out in substantially the same manner as Process 8, and therefore the reaction mode and reaction condition (e.g. solvent, reaction temperature, etc.) of this reaction are to be referred to those as explained in Process 8.

#### Process 22

The object compound (I-7) or its salt can be prepared by reacting a compound (I-6) or its salt with an acylating agent.

Suitable salts of the compounds (I-6) and (I-7) may be the same as those exemplified for the compound (I).

This reaction can be carried out in substantially the same manner as Process 6, and therefore the reaction mode and

reaction condition (e.g. solvent, reaction temperature, etc.) of this reaction are to be referred to those as explained in Process 6.

5     Process 23

The object compound (I-8) or its salt can be prepared by reacting a compound (I-6) or its salt with lower alkanal in the presence of a reducing agent.

10     Suitable salts of the compounds (I-6) and (I-8) may be the same as those exemplified for the compound (I).

Suitable lower alkanal may be C<sub>1</sub>-C<sub>6</sub> alkanal such as formaldehyde, ethanal, propanal or the like, in which preferable one is formaldehyde.

15     Suitable reducing agent may be diborane, borane-organic amine complex [e.g. borane-pyridine complex, etc.], alkali metal cyanoborohydride [e.g. sodium cyanoborohydride, lithium cyanoborohydride, etc.], sodium borohydride and the like.

The reaction is preferably carried out in the presence of molecular sieves.

20     The reaction is usually carried out in a conventional solvent such as water, an alcohol [e.g. methanol, ethanol, etc.], dioxane, tetrahydrofuran, a mixture thereof or any other organic solvent which does not adversely influence the reaction.

25     The reaction may also be carried out in an acidic condition [e.g. presence of acetic acid, sulfuric acid, etc.] and the reaction temperature is not critical, and the reaction is usually carried out under cooling to warming.

30     Process 24.

The object compound (I-10) or its salt can be prepared by subjecting a compound (I-9) or its salt to reduction.

Suitable salts of the compounds (I-9) and (I-10) may be the same as those exemplified for the compound (I).

35     The reduction may include chemical reduction and

catalytic reduction, which are carried out in a conventional manner.

Suitable reducing agents to be used in chemical reduction are a metal [e.g. tin, zinc, iron, nickel, etc.],  
5 a combination of such metal and/or metallic compound [e.g. nickel chloride, chromium chloride, chromium acetate, etc.] and an organic or inorganic acid [e.g. formic acid, acetic acid, propionic acid, trifluoroacetic acid, p-toluenesulfonic acid, hydrochloric acid, hydrobromic acid, etc.],  
10 a combination of such metal and/or metallic compound and base [e.g. ammonia, ammonium chloride, sodium hydroxide, etc.], a metal hydride compound such as aluminum hydride compound [e.g. lithium aluminum hydride, sodium aluminum hydride, aluminum hydride, lithium trimethoxyaluminum hydride, lithium  
15 tri-t-butoxyaluminum hydride, etc.], borohydride compound [e.g. sodium borohydride, lithium borohydride, sodium cyanoborohydride, tetramethylammonium borohydride, borane, diborane, etc.], a phosphorus compound [e.g. phosphorus trichloride, phosphorus tribromide, triphenylphosphine, triethylphosphine, etc.] and the like.

Suitable catalysts to be used in catalytic reduction are conventional ones such as platinum catalysts [e.g. platinum plate, spongy platinum, platinum black, colloidal platinum, platinum oxide, platinum wire, etc.], palladium catalyst  
25 [e.g. spongy palladium, palladium black, palladium oxide, palladium on carbon, colloidal palladium, palladium on barium sulfate, palladium on barium carbonate, etc.], nickel catalyst [e.g. reduced nickel, nickel oxide, Raney nickel, etc.], cobalt catalyst [e.g. reduced cobalt, Raney cobalt, etc.],  
30 iron catalyst [e.g. reduced iron, Raney iron, etc.], copper catalyst [e.g. reduced copper, Raney copper, Ullman copper, etc.], or the like.

The reduction is usually carried out in a solvent. A suitable solvent to be used may be water, an alcohol [e.g.  
35 methanol, ethanol, propanol, etc.], acetonitrile or any other



conventional organic solvent such as dimethyl ether, dioxane, tetrahydrofuran, etc. or a mixture thereof.

The reaction temperature is not critical, and the reaction is preferably carried out under cooling to heating.

5

#### Process 25

The object compound (I-10) or its salt can be prepared by reacting a compound (I-11) or its salt with an azide compound.

10        Suitable salts of the compounds (I-10) and (I-11) may be the same as those exemplified for the compound (I).

      Suitable azide compound may be sodium azide, diphenylphosphorylazide and the like.

15        The reaction is usually carried out in a conventional solvent such as water, tetrahydrofuran, dioxane or any other organic solvent which does not adversely influence the reaction, or a mixture thereof.

20        The reaction is also preferably carried out in the presence of a conventional base such as triethylamine, pyridine or the like.

      The reaction temperature is not critical, and the reaction is preferably carried out under warming to heating.

#### Process 26

25        The object compound (I-13) or its salt can be prepared by reacting a compound (I-12) or its reactive derivative at the carboxy group or a salt thereof with a reducing agent.

30        Suitable salts of the compounds (I-13), (I-12) and its reactive derivative at the carboxy group may be the same as those exemplified for the compound (I).

      Suitable reactive derivative at the carboxy group of the compound (I-12) may include an activated imide (e.g. phthalimido, etc.), an activated amide, an activated ester and the like.

35        Suitable reducing agent may be aluminum hydride compound

[e.g. lithium aluminum hydride, lithium tri-*t*-butoxyaluminum hydride, etc.], borohydride compound [e.g. lithium borohydride, etc.], aluminum alkoxide [e.g. aluminum isopropoxide, etc.] and the like.

5       The reaction is usually carried out in a conventional solvent, such as diethyl ether, dioxane, or any other organic solvent which does not adversely influence the reaction, or a mixture thereof.

10       The reaction temperature is not critical, and the reaction is usually carried out under cooling to heating.

#### Process 27

15       The object compound (I-15) or its salt can be prepared by reacting a compound (I-14) or its salt with an acylating agent.

Suitable salts of the compounds (I-14) and (I-15) may be the same as those exemplified for the compound (I).

20       This reaction can be carried out in substantially the same manner as Process 6, and therefore the reaction mode and reaction condition (e.g. solvent, reaction temperature, etc.) of this reaction are to be referred to those as explained in Process 6.

#### Process 28

25       The object compound (I-16) or its salt can be prepared by reacting a compound (I-15) or its salt with an alkali metal salt of phthalimide.

Suitable salts of the compounds (I-15) and (I-16) may be the same as those exemplified for the compound (I).

30       Suitable alkali metal salt of phthalimide may be potassium phthalimide and the like.

35       The reaction is usually carried out in a conventional solvent such as dimethyl sulfoxide, tetrahydrofuran or any other solvent which does not adversely influence the reaction.

The reaction temperature is not critical, and the reaction can be carried out under cooling to heating.

#### Process 29

5       The object compound (I-18) or its salt can be prepared by reacting a compound (I-17) or its salt with an amine.

Suitable salts of the compounds (I-17) and (I-18) may be the same as those exemplified for the compound (I).

10       Suitable amine may be N-lower alkylpiperazine, morpholine, dimethylamine, di(lower)alkylaminopiperidine, di(lower)alkylhydrazine, amino(lower)alkyl(N-lower alkyl)-amine, di(lower)alkylamino(lower)alkylamine and the like.

15       The reaction is carried out in no solvent or a solvent such as tetrahydrofuran, dioxane or any other solvent which does not adversely influence the reaction.

The reaction temperature is not critical, and the reaction is preferably carried out under warming to heating.

#### Process 30

20       The object compound (I-20) or its salt can be prepared by subjecting a compound (I-19) or its salt to elimination reaction of N-protective group.

Suitable salts of the compounds (I-19) and (I-20) may be the same as those exemplified for the compound (I).

25       This reaction can be carried out in substantially the same manner as Process 8, and therefore the reaction mode and reaction condition (e.g. solvent, reaction temperature, etc.) of this reaction are to be referred to those as explained in Process 8.

30

#### Process 31

The object compound (I-22) or its salt can be prepared by reacting a compound (I-21) with hydroxylamine or its salt.

35       Suitable salts of the compounds (I-21) and (I-22) may be the same as those exemplified for the compound (I).

Suitable salt of hydroxylamine may be an acid addition salt as exemplified for the compound (I).

The reaction is preferably carried out in the presence of a conventional base such as sodium acetate, sodium  
5 hydrogen carbonate or the like.

The reaction is usually carried out in a solvent which does not influence the reaction such as water, an alcohol (e.g. methanol, ethanol, etc.), pyridine or a mixture thereof.

10 The reaction temperature is not critical and the reaction is preferably carried out warming to heating.

#### Process 32

The object compound (I-23) or its salt can be prepared  
15 by reacting a compound (VI) or its reactive derivative at the carboxy group or a salt thereof with a compound (VII) or its salt.

Suitable salts of the compounds (I-23), (VII), (VI) and its reactive derivative at the carboxy group may be the same  
20 as those exemplified for the compound (I).

This reaction can be carried out in substantially the same manner as Process 1, and therefore the reaction mode and reaction condition (e.g. solvent, reaction temperature, etc.) of this reaction are to be referred to those as explained in  
25 Process 1.

The compounds obtained by the above processes can be isolated and purified by a conventional method such as pulverization, recrystallization, column chromatography,  
30 reprecipitation, or the like.

It is to be noted that the compound (I) and the other compounds may include one or more stereoisomer(s) such as optical isomer(s) or geometrical isomer(s) due to asymmetric carbon atom(s) and double bond(s), and all of such isomers  
35 and mixture thereof are included within the scope of this

invention.

Additionally, it is to be noted that any hydrate of the compound (I) is also included within the scope of this invention.

5       The object compound (I) and pharmaceutically acceptable salts thereof possess activities as vasopressin antagonistic activity, vasodilating activity, hypotensive activity, activity for inhibiting saccharide release in liver, activity for inhibiting growth of mesangium cells, water diuretic  
10 activity, platelet agglutination inhibitory activity, oxytocin antagonistic activity and the like, and are useful for the treatment and/or prevention of hypertension, heart failure, renal insufficiency, edema, ascites, vasopressin parasecretion syndrome, hepatocirrhosis, hyponatremia,  
15 hypokalemia, diabetic, circulation disorder, cerebrovascular disease (e.g. cerebral edema, cerebral infarction, etc.), Meniere's syndrome (e.g. Meniere's disease, etc.), motion sickness and the like in human being and animals.

20       In order to illustrate the usefulness of the object compound (I), the pharmacological data of the compound (I) are shown in the following.

#### Test 1

25

#### Vasopressin 1 (V1) receptor binding

##### (i) Test Method :

Blood was obtained by venipuncture from normal subjects.  
30 Platelet-rich plasma (PRP) was prepared by centrifugation of whole blood at 200 xg for 10 minutes. PRP was centrifuged at 45,000 xg for 30 minutes. The remaining pellet was resuspended in 10 volume of ice cold 100 mM Tris-HCl (pH 7.4) buffer (containing 5 mM MgCl<sub>2</sub>, 0.1% bovine serum albumin and  
35 1 mM EDTA), and centrifuged at 45,000 xg for 30 minutes

again. The final pellet was resuspended in 100 mM Tris-HCl buffer. The resulting membrane preparation was used immediately for the binding assay.

Competition assays were conducted at equilibrium (15 minutes at 30°C) by using 1.5 nM  $^3\text{H}$ -vasopressin (40-87 Ci/mmol; New England Nuclear) in 100 mM Tris-HCl (pH 7.4) buffer. Nonspecific binding was determined by using 1  $\mu\text{M}$  vasopressin. After incubation, reaction was terminated by adding 5 ml of ice-cold 100 mM Tris-HCl (pH 7.4) buffer, and then filtered rapidly through Whatman glass filter (GF/C). The filter was washed twice with the same buffer. The glass filter was mixed with liquid scintillation cocktail, and radioactivity was counted in a liquid scintillation counter. Competition activity of the test compound was represented by  $\text{IC}_{50}$  values.

(ii) Test Result :

Test Compound (Example No.)	$\text{IC}_{50}$ (nM)
39-27)	1.5
39-35)	<1.0
115-71)	0.7
115-81)	4.5

Test 2

Vasopressin 2 (V2) receptor binding

(i) Test Method :

For binding assays, the receptor cDNA was permanently expressed in Chinese hamster ovary (CHO) cells. CHO cells were transfected with a vector directing expression of the cDNA for the human V2 receptor and the clonal cell lines

expressing human V2 receptor was established essentially as described previously (Nakajima, Y., et. al. J. Biol. Chem., 1992, 267, 2437).

DNA-transfected cells were harvested and homogenized in ice cold 250 mM sucrose buffer containing 25 mM Tris-HCl (pH 7.4), 10 mM MgCl<sub>2</sub>, 1 mM EDTA and 5 µg/ml p-amidinophenylmethylsulfonyl fluoride (A-PMSF). The homogenate was centrifuged at 500 xg for 10 minutes. The supernatant was centrifuged at 100,000 xg for 1 hour. The final pellet was suspended in 25 mM Tris-HCl (pH 7.4) buffer (containing 10 mM MgCl<sub>2</sub>, 1 mM EDTA and 5 µg/ml A-PMSF), and stored in small aliquots at -80°C.

Competition assays were conducted at equilibrium (2 hours at 22°C) by using 0.5 nM <sup>3</sup>H-vasopressin (40-87 Ci/mmol, New England Nuclear) in 100 mM Tris-HCl (pH 7.4) buffer (containing 5 mM MgCl<sub>2</sub>, 5 µg/ml A-PMSF, 4 µg/ml leupeptin, 40 µg/ml bacitracin, 20 µg/ml chymostatin and 0.1% bovine serum albumin). Nonspecific binding was determined by using 1 µM vasopressin. After incubation, reaction mixture was rapidly filtered through Whatman glass filter (GF/C). The filter was washed twice with the same buffer. The radioactivity was counted in a liquid scintillation counter. Competition activity of the test compound was represented by IC<sub>50</sub> values.

(ii) Test Result :

Test Compound (Example No.)	IC <sub>50</sub> (nM)
39-27)	460
39-35)	380

For therapeutic purpose, the compound (I) of the present invention can be used in a form of pharmaceutical preparation containing one of said compounds, as an active ingredient, in

admixture with a pharmaceutically acceptable carrier such as an organic or inorganic solid, semi-solid or liquid excipient suitable for oral, parenteral or external(topical) administration. The pharmaceutical preparations may be capsules, tablets, dragees, granules, suppositories, solution, lotion, suspension, emulsion, ointment, gel, or the like. If desires, there may be included in these preparations, auxiliary substances, stabilizing agents, wetting or emulsifying agents, buffers and other commonly used additives.

While the dosage of the compound (I) will vary depending upon the age and condition of the patient, an average single dose of about 0.1 mg, 1 mg, 10 mg, 50 mg, 100 mg, 250 mg, 500 mg and 1000 mg of the compound (I) may be effective for treating the above-mentioned diseases. In general, amounts between 0.1 mg/body and about 1,000 mg/body may be administered per day.

The following Preparations and Examples are given for the purpose of illustrating this invention.

- to be continued on the next page -



Preparation 1

To a suspension of sodium hydride (133 mg) in tetrahydrofuran (5.0 ml) was added dropwise a solution of benzyl indole-4-carboxylate (580 mg) in tetrahydrofuran (5.0 ml) at 0°C and the mixture was stirred at 0°C for 1 hour. 4-Toluenesulfonyl chloride (440 mg) was added to the mixture and the solution was stirred at ambient temperature for 1 hour. The reaction was quenched with 1N hydrochloric acid and then the aqueous solution was extracted with ethyl acetate. Drying, filtering and removal of solvents afforded a crude product. The crude product was purified by column chromatography (eluent; n-hexane:ethyl acetate = 15:1) to give benzyl 1-(4-toluenesulfonyl)indole-4-carboxylate (560 mg) as a colorless syrup.

NMR (CDCl<sub>3</sub>, δ) : 2.32 (3H, s), 5.39 (2H, s), 7.19-7.23 (2H, m), 7.31-7.48 (7H, m), 7.67 (1H, d, J=4Hz), 7.72 (2H, d, J=9Hz), 8.00 (1H, d, J=8Hz), 8.20 (1H, d, J=8Hz)

Preparation 2

To a suspension of sodium hydride (174 mg) in tetrahydrofuran (8.0 ml) was added dropwise a solution of benzyl indole-7-carboxylate (700 mg) in tetrahydrofuran (7.0 ml) at 0°C and the mixture was stirred at 0°C for 1 hour. Chloromethyl pivalate (461 mg) was added to the mixture and the solution was stirred at ambient temperature for 3 hours. The reaction was quenched with 1N hydrochloric acid and then the aqueous solution was extracted with ethyl acetate. Drying, filtering and removal of solvents afforded benzyl 1-pivaloyloxymethylindole-7-carboxylate (1.08 g) as a yellow oil.

NMR (CDCl<sub>3</sub>, δ) : 1.01 (9H, s), 5.42 (2H, s), 6.40 (2H, s), 6.58 (1H, d, J=4Hz), 7.17 (1H, t, J=8Hz), 7.28 (1H, d, J=4Hz), 7.33-7.42 (3H, m), 7.47-7.51 (2H, m), 7.73-7.80 (2H, m)

Preparation 3

To a solution of 2,2,6,6-tetramethylpiperidine (322 mg) in tetrahydrofuran (5.0 ml) was added dropwise a solution of n-butyllithium (1.6M n-hexane solution 1.3 ml) at -70 ~ -60°C and the solution was stirred at 0°C for 30 minutes.

A solution of benzyl 1-tert-butoxycarbonylindole-4-carboxylate (500 mg) in tetrahydrofuran (2.5 ml) was added dropwise to the above solution at -70 ~ -60°C and the mixture was stirred at -70°C for 30 minutes. To the mixture was added a solution of ethyl chloroformate (185 mg) in tetrahydrofuran (2.5 ml) at such a rate as to maintain the temperature below -60°C. The solution was stirred at -70°C for 2 hours and the reaction was quenched with aqueous saturated ammonium chloride solution at -20°C. The aqueous solution was extracted with ethyl acetate. Drying, filtering and removal of solvents afforded a crude product. The crude product was chromatographed on silica gel (eluent; n-hexane:ethyl acetate = 15:1) to give benzyl 1-tert-butoxycarbonyl-2-ethoxycarbonylindole-4-carboxylate (100 mg) as a colorless oil.

NMR (CDCl<sub>3</sub>, δ) : 1.39 (3H, t, J=7Hz), 1.62 (9H, s), 4.38 (2H, q, J=7Hz), 5.43 (2H, s), 7.31-7.50 (6H, m), 7.78 (1H, s), 8.04 (1H, d, J=8Hz), 8.32 (1H, d, J=9Hz)

Preparation 4

To a solution of 2-amino-3-nitrobenzoic acid (4.47 g) in 1,2-dichloroethane (50 ml) was added trifluoroacetic anhydride (10.3 g) at 5°C and the mixture was stirred at ambient temperature for 5 hours. To the mixture was added trifluoroacetic anhydride (5.15 g) and it was stirred at ambient temperature for additional 1 hour. The solution was concentrated in vacuo to give 8-nitro-2-trifluoromethyl-3,1-benzoxazin-4-one as a slight yellow powder (6.35 g).

NMR (CDCl<sub>3</sub>, δ) : 7.86 (1H, t, J=7Hz), 8.29 (1H, d,

J=7Hz), 8.51 (1H, d, J=7Hz)

#### Preparation 5

To a solution of ethyl 2-(N-benzylamino)-3-nitrobenzoate  
5 (400 mg) in N,N-dimethylaniline (3 ml) was added  
methoxyacetyl chloride (318 mg) at ambient temperature and  
the mixture was stirred at 90°C for 4 hours. The reaction  
mixture was poured into water and the aqueous solution was  
10 extracted with ethyl acetate. The organic layer was washed  
successively with 1N hydrochloric acid, water and brine and  
the solution was dried over magnesium sulfate. The solvent  
was evaporated in vacuo and the residue was chromatographed  
on silica gel eluting with a mixture of n-hexane and ethyl  
acetate (3:1) to give ethyl 2-(N-benzyl-N-methoxyacetyl)-  
15 amino-3-nitrobenzoate (480 mg) as an oil.

NMR (CDCl<sub>3</sub>, δ) : 1.29 (3H, t, J=7Hz), 3.37 (3H, s),  
3.92 (2H, s), 4.09 (2H, q, J=7Hz), 4.74 (1H, d,  
J=13Hz), 4.83 (1H, d, J=13Hz), 7.00-7.11 (2H, m),  
7.11-7.31 (3H, m), 7.59 (1H, t, J=8Hz), 7.96 (1H,  
20 d, J=8Hz), 8.08 (1H, d, J=8Hz)

#### Preparation 6

A mixture of 2,3-diaminotoluene (2.0 g) and ethyl  
N-methyloxamate (2.36 g) in N,N-dimethylformamide (10 ml) was  
25 stirred at 175°C for 8 hours. After being cooled to ambient  
temperature, the mixture was poured into a mixture of  
saturated aqueous sodium bicarbonate solution and ethyl  
acetate and the organic layer was separated. The organic  
layer was washed with brine and the solution was dried over  
30 magnesium sulfate. The solvent was evaporated in vacuo and  
the residue was chromatographed on silica gel eluting with a  
mixture of chloroform and methanol (50:1) to give 4-methyl-2-  
(N-methylcarbamoyl)-1H-benzimidazole (1.17 g) as a powder.

NMR (CDCl<sub>3</sub>, δ) : 2.60 (3H x 1/2, s), 2.66 (3H x 1/2,  
35 s), 3.10 (3H x 1/2, s), 3.12 (3H x 1/2, s), 7.06-

7.19 (1H, m), 7.19-7.29 (1H, m), 7.36 (1H x 1/2, d, J=8Hz), 7.61 (1H x 1/2, d, J=8Hz), 7.71 (1H, br peak)

5     Preparation 7

To a suspension of 4-methyl-2-(N-methylcarbamoyl)-1H-benzimidazole (1.0 g) in 1N-aqueous sodium hydroxide solution (15 ml) was added portionwise potassium permanganate (3.34 g) at 100°C and the reaction mixture was stirred at the same  
10     temperature for 15 minutes. The reaction mixture was filtered through a bed of celite and the filtrate was washed with chloroform. The aqueous layer was adjusted to pH 3 with 4N hydrochloric acid. The precipitate was collected by vacuum filtration to give 2-(N-methylcarbamoyl)-1H-  
15     benzimidazole-4-carboxylic acid (647 mg) as a solids.

NMR (DMSO-d<sub>6</sub>, δ) : 2.85 (3H, d, J=5Hz), 7.41 (1H, t, J=8Hz), 7.90 (1H, d, J=8Hz), 7.95 (1H, d, J=8Hz), 9.06 (1H, q-like)

20     Preparation 8

To a solution of methyl 2-hydroxymethyl-1H-benzimidazole-4-carboxylate (1.0 g) in N,N-dimethylformamide (10 ml) were added tert-butylchlorodiphenylsilane (1.87 g) and imidazole (495 mg) at ambient temperature and the mixture  
25     was stirred at the same temperature for 28 hours. The reaction mixture was poured into water and the aqueous solution was extracted with ethyl acetate. The organic layer was washed with water and brine and dried over magnesium sulfate. The solvent was evaporated in vacuo and the residue  
30     was chromatographed on silica gel eluting with a mixture of n-hexane and ethyl acetate (10:1) to give methyl 2-tert-butylidiphenylsiloxymethyl-1H-benzimidazole-4-carboxylate (1.45 g) as an oil.

NMR (CDCl<sub>3</sub>, δ) : 1.18 (9H, s), 4.02 (3H, s), 5.06 (2H, s), 7.30 (1H, t, J=8Hz), 7.35-7.50 (6H, m), 7.67-

35

7.73 (4H, m), 7.89 (1H, d, J=8Hz), 7.92 (1H, d, J=8Hz)

#### Preparation 9

5 To a solution of methyl 2-tert-butyldiphenylsiloxy-methyl-1H-benzimidazole-4-carboxylate (500 mg) in pyridine (3 ml) was added lithium iodide (602 mg) under nitrogen at ambient temperature and the mixture was heated to reflux for 3 hours. The reaction mixture was concentrated in vacuo and  
10 the residue was dissolved in chloroform. The solution was washed with water and brine and the organic layer was dried over magnesium sulfate. The solvent was evaporated in vacuo and the residue was chromatographed on silica gel eluting with a mixture of chloroform and methanol (chloroform only-  
15 50:1-25:1-10:1) to give 2-tert-butyldiphenylsiloxymethyl-1H-benzimidazole-4-carboxylic acid (425 mg) as a powder.

NMR (DMSO-d<sub>6</sub>, δ) : 1.03 (9H, s), 5.00 (2H, s), 7.28 (1H, t, J=8Hz), 7.38-7.52 (6H, m), 7.70-7.75 (4H, m), 7.80 (1H, d, J=8Hz), 7.91 (1H, d, J=8Hz)

20

#### Preparation 10

The mixture of benzyl 1-(4-toluenesulfonyl)indole-4-carboxylate (550 mg) and 10% palladium on charcoal (200 mg) in methanol (20 ml) and water (2 ml) was hydrogenated at  
25 ambient temperature (an initial hydrogen pressure was set to 3.5 atm.). The theoretical amount of hydrogen was absorbed in 6 hours. The resulting mixture was filtered through a bed of celite and the filtrate was evaporated in vacuo. The residue was diluted with chloroform and the solution was  
30 dried over magnesium sulfate. Filtering and removal of solvents afforded a crude product. The crude product was triturated with diethyl ether-n-hexane (1:3) to give 1-(4-toluenesulfonyl)indole-4-carboxylic acid (330 mg) as a brown powder.

35 NMR (DMSO-d<sub>6</sub>, δ) : 2.32 (3H, s), 7.30 (1H, d, J=4Hz),

7.37-7.43 (2H, m), 7.47 (1H, d, J=8Hz), 7.89 (3H, d, J=8Hz), 7.97 (1H, d, J=4Hz), 8.20 (1H, d, J=8Hz)

### Preparation 11

5       The following compounds were obtained according to a similar manner to that of Preparation 10.

1) 1-Pivaloyloxymethylindole-7-carboxylic acid

10       NMR (DMSO-d<sub>6</sub>, δ) : 1.00 (9H, s), 6.40 (2H, s), 6.61 (1H, d, J=3Hz), 7.16 (1H, t, J=8Hz), 7.53 (1H, d, J=3Hz), 7.60 (1H, d, J=8Hz), 7.78 (1H, d, J=8Hz)

2) 1-Methylindole-7-carboxylic acid

15       NMR (CDCl<sub>3</sub>, δ) : 3.88 (3H, s), 6.52 (1H, d, J=4Hz), 7.00-7.12 (2H, m), 7.72-7.79 (2H, m)

### Preparation 12

To a mixture of 10% palladium on charcoal (130 mg) in 5.0% formic acid-methanol (5.0 ml) was added a solution of benzyl 1-tert-butoxycarbonyl-2-ethoxycarbonylindole-4-carboxylate (130 mg) in 5.0% formic acid-methanol (5.0 ml). The mixture was stirred under nitrogen atmosphere at ambient temperature for 30 minutes. The resulting mixture was filtered through a bed of celite and the filtrate was evaporated in vacuo to give 1-tert-butoxycarbonyl-2-ethoxycarbonylindole-4-carboxylic acid (87 mg) as a white crystal.

25       NMR (CDCl<sub>3</sub>, δ) : 1.44 (3H, t, J=7Hz), 1.66 (9H, s), 4.42 (2H, q, J=7Hz), 7.50 (1H, t, J=9Hz), 7.83 (1H, s), 8.12 (1H, d, J=9Hz), 8.39 (1H, d, J=9Hz)

### Preparation 13

To an ice water bath cooled 4N hydrogen chloride solution in 1,4-dioxane (5 ml) was added 2-(N-tert-butoxycarbonyl-N-methyl)amino-3-nitrobenzoic acid (900 mg)

and the solution was stirred at ambient temperature for 2 hours. The reaction mixture was concentrated in vacuo and the residue was washed with diethyl ether and collected by vacuum filtration to give 2-(N-methylamino)-3-nitrobenzoic acid hydrochloride (687 mg) as a powder.

NMR (DMSO-d<sub>6</sub>, δ) : 2.70 (3H, s), 6.73 (1H, t, J=8Hz), 7.98 (1H, d, J=8Hz), 8.04 (1H, d, J=8Hz)

#### Preparation 14

The following compound was obtained according to a similar manner to that of Preparation 13.

Ethyl 2-(N-benzylamino)-3-nitrobenzoate

NMR (CDCl<sub>3</sub>, δ) : 1.38 (3H, t, J=7Hz), 4.16 (2H, d, J=6Hz), 4.35 (2H, q, J=7Hz), 6.72 (1H, t, J=8Hz), 7.22-7.46 (5H, m), 8.00 (1H, d, J=8Hz), 8.11 (1H, d, J=8Hz), 8.80 (1H, br s)

#### Preparation 15

To a suspension of sodium hydride (60% dispersion in mineral oil, 142 mg) in N,N-dimethylformamide (1 ml) was added dropwise a solution of ethyl 2-(N-tert-butoxycarbonyl)amino-3-nitrobenzoate (1.0 g) in N,N-dimethylformamide (5 ml) under nitrogen in ice water bath and stirred at the same temperature for 1 hour. To the mixture was added methyl iodide (526 mg) at 0°C under nitrogen and the solution was stirred at the same temperature for 2 hours. The reaction mixture was poured into water and the aqueous solution was extracted with ethyl acetate. The organic layer was washed with water and brine, dried over magnesium sulfate and the solvent was evaporated to give ethyl 2-(N-tert-butoxycarbonyl-N-methyl)amino-3-nitrobenzoate (1.05 g) as an oil.

NMR (CDCl<sub>3</sub>, δ) : 1.28 (9H, s), 1.41 (3H, t, J=7.5Hz), 3.10-3.20 (3H, m), 4.30-4.48 (2H, m), 7.52 (1H, t,

J=8Hz), 7.95 (1H, d, J=8Hz), 8.10 (1H, d, J=8Hz)

#### Preparation 16

5 The following compounds were obtained according to a similar manner to that of Preparation 15.

- 1) Ethyl 2-(N-benzyl-N-tert-butoxycarbonyl)amino-3-nitrobenzoate

10 NMR (CDCl<sub>3</sub>, δ) : 1.17-1.38 (12H, m), 4.08-4.23 (2H, m), 4.53 (1H, d, J=13Hz), 4.81 (1H, d, J=13Hz), 7.03-7.16 (2H, m), 7.16-7.29 (3H, m), 7.45 (1H, t, J=8Hz), 7.88 (1H, d, J=8Hz), 8.04 (1H, d, J=8Hz)

- 2) 3-(N-Acetyl-N-methyl)amino-2-nitrobenzoic acid

15 NMR (CDCl<sub>3</sub>, δ) : 1.87 (3H, s), 3.20 (3H, s), 7.55 (1H, d, J=8Hz), 7.69 (1H, t, J=8Hz), 8.20 (1H, d, J=8Hz)

- 3) 3-(N-Acetyl-N-ethyl)amino-2-nitrobenzoic acid

20 NMR (DMSO-d<sub>6</sub>, δ) : 1.00 (3H, t, J=7Hz), 1.72 (3H, s), 3.08 (1H, m), 3.86 (1H, m), 7.78-7.91 (2H, m), 8.12 (1H, d, J=8Hz)

#### Preparation 17

25 To a solution of ethyl 2-(N-tert-butoxycarbonyl-N-methyl)amino-3-nitrobenzoate (1.0 g) in ethanol (10 ml) was added 1N aqueous sodium hydroxide solution (3.5 ml) and the solution was stirred at ambient temperature for 1 day. The reaction mixture was concentrated and the residue was dissolved in water. The aqueous layer was washed with  
30 diethyl ether and the aqueous solution was adjusted to pH 4 with 1N hydrochloric acid. The solution was extracted with chloroform and the organic layer was separated. The solution was washed with water and brine and the solution was dried over magnesium sulfate. The solvent was evaporated in vacuo  
35 to give 2-(N-tert-butoxycarbonyl-N-methyl)amino-3-



nitrobenzoic acid (910 mg) as a powder.

NMR (CDCl<sub>3</sub>,  $\delta$ ) : 1.26 (9H, s), 3.20 (3H, s), 7.55 (1H, t, J=8Hz), 8.00 (1H, d, J=8Hz), 8.22 (1H, d, J=8Hz)

5' Preparation 18

The following compounds were obtained according to a similar manner to that of Preparation 17.

1) 3-Benzyl-2-methoxymethyl-3H-benzimidazole-4-carboxylic acid

NMR (DMSO-d<sub>6</sub>,  $\delta$ ) : 3.40 (3H, s), 4.75 (2H, s), 5.95 (2H, s), 6.83-6.91 (2H, m), 7.16-7.26 (3H, m), 7.33 (1H, t, J=8Hz), 7.72 (1H, d, J=8Hz), 7.89 (1H, d, J=8Hz)

2) 1,2-Dimethyl-1H-benzimidazole-4-carboxylic acid

NMR (DMSO-d<sub>6</sub>,  $\delta$ ) : 2.64 (3H, s), 3.82 (3H, s), 7.37 (1H, t, J=8Hz), 7.76 (1H, d, J=8Hz), 7.86 (1H, d, J=8Hz)

3) 1-Ethyl-2-methyl-1H-benzimidazole-4-carboxylic acid

NMR (DMSO-d<sub>6</sub>,  $\delta$ ) : 1.33 (3H, t, J=7Hz), 2.68 (3H, s), 4.33 (2H, q, J=7Hz), 7.37 (1H, t, J=8Hz), 7.78 (1H, d, J=8Hz), 7.90 (1H, d, J=8Hz)

4) 2-Methyl-1-propyl-1H-benzimidazole-4-carboxylic acid

NMR (DMSO-d<sub>6</sub>,  $\delta$ ) : 0.94 (3H, t, J=7Hz), 1.82 (2H, m), 2.88 (3H, s), 4.41 (2H, t, J=7Hz), 7.65 (1H, t, J=8Hz), 8.05 (1H, d, J=8Hz), 8.24 (1H, d, J=8Hz)

5) 1-(4-Methoxybenzyl)-2-(N-methylcarbamoyl)-1H-benzimidazole-4-carboxylic acid

NMR (CD<sub>3</sub>OD,  $\delta$ ) : 2.96 (3H, s), 3.72 (3H, s), 6.00 (2H, s), 6.83 (2H, d, J=8Hz), 7.20 (2H, d, J=8Hz), 7.45 (1H, t, J=8Hz), 7.84 (1H, d, J=8Hz), 8.03 (1H, d,

J=8Hz)

#### Preparation 19

To a solution of ethyl 2-(N-benzyl-N-methoxyacetyl)amino-3-nitrobenzoate (478 mg) in ethanol (5 ml) were added iron powder (358 mg) and acetic acid (771 mg) and the mixture was refluxed for 2 hours. The reaction mixture was filtered through a bed of celite and the filtrate was concentrated in vacuo. The residue was diluted with a mixture of ethyl acetate and saturated aqueous sodium bicarbonate solution and the mixture was filtered through a bed of celite again. The organic layer was separated and washed with water and brine. The solution was dried over magnesium sulfate and the solvent was evaporated in vacuo to give ethyl 3-benzyl-2-methoxymethyl-3H-benzimidazole-4-carboxylate (364 mg) as an oil.

NMR (CDCl<sub>3</sub>, δ) : 1.20 (3H, t, J=7Hz), 3.40 (3H, s), 4.15 (2H, q, J=7Hz), 4.75 (2H, s), 5.91 (2H, s), 6.78-6.89 (2H, m), 7.14-7.41 (4H, m), 7.68 (1H, d, J=8Hz), 7.98 (1H, d, J=8Hz)

#### Preparation 20

The following compound was obtained according to a similar manner to that of Preparation 19.

Methyl 2-methyl-1H-benzimidazole-4-carboxylate

NMR (CDCl<sub>3</sub>, δ) : 2.67 (3H, s), 4.00 (3H, s), 7.25 (1H, t, J=8Hz), 7.85 (1H, d, J=8Hz), 7.89 (1H, d, J=8Hz)

#### Preparation 21

The following compounds were obtained by using methyl 3-(N-acetyl-N-methyl)amino-2-nitrobenzoate as a starting compound according to a similar manner to that of Preparation 19.

A mixture of methyl 1,2-dimethyl-1H-benzimidazole-4-carboxylate and ethyl 1,2-dimethyl-1H-benzimidazole-4-carboxylate

5           Methyl 1,2-dimethyl-1H-benzimidazole-4-carboxylate  
NMR (CDCl<sub>3</sub>, δ) : 2.69 (3H, s), 3.75 (3H, s), 4.02 (3H, s), 7.28 (1H, t, J=8Hz), 7.48 (1H, d, J=8Hz), 7.95 (1H, d, J=8Hz)

10           Ethyl 1,2-dimethyl-1H-benzimidazole-4-carboxylate  
NMR (CDCl<sub>3</sub>, δ) : 1.44 (3H, t, J=7Hz), 2.67 (3H, s), 3.72 (3H, s), 4.48 (2H, q, J=7Hz), 7.26 (1H, t, J=8Hz), 7.45 (1H, d, J=8Hz), 7.90 (1H, d, J=8Hz)

15           Preparation 22

The following compound was obtained by using methyl 2-(N-acetyl-N-ethyl)amino-3-nitrobenzoate as a starting compound according to a similar manner to that of Preparation 19.

20

Ethyl 1-ethyl-2-methyl-1H-benzimidazole-4-carboxylate  
NMR (CDCl<sub>3</sub>, δ) : 1.37 (3H, t, J=7Hz), 1.43 (3H, t, J=7Hz), 2.66 (3H, s), 4.19 (2H, q, J=7Hz), 4.48 (2H, q, J=7Hz), 7.25 (1H, t, J=8Hz), 7.47 (1H, d, J=8Hz), 7.89 (1H, d, J=8Hz)

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Preparation 23

To a solution of 3-(N-acetyl-N-methyl)amino-2-nitrobenzoic acid (700 mg) in 20% methanol in benzene solution (5 ml) was added dropwise 2N trimethylsilyldiazomethane in n-hexane solution (5 ml) in ice water bath and the mixture was allowed to stand at ambient temperature for 1 hour. The reaction mixture was concentrated in vacuo and the residue was dissolved in ethyl acetate. The solution was washed successively with saturated

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aqueous sodium bicarbonate solution, water and brine and the organic layer was dried over magnesium sulfate. The solvent was evaporated in vacuo and the residue was chromatographed on silica gel eluting with a mixture of n-hexane - ethyl acetate (10:1) to give methyl 3-(N-acetyl-N-methyl)amino-2-nitrobenzoate (547 mg) as an oil.

NMR (CDCl<sub>3</sub>, δ) : 1.85 (3H, s), 3.19 (3H, s), 3.94 (3H, s), 7.54 (1H, d, J=8Hz), 7.68 (1H, t, J=8Hz), 8.13 (1H, d, J=8Hz)

#### Preparation 24

The following compounds were obtained according to a similar manner to that of Preparation 23.

1) Methyl 3-(N-acetyl-N-ethyl)amino-2-nitrobenzoate

NMR (CDCl<sub>3</sub>, δ) : 1.11 (3H, t, J=7Hz), 1.83 (3H, s), 3.20 (1H, m), 3.93 (3H, s), 4.10 (1H, m), 7.49 (1H, d, J=8Hz), 7.67 (1H, t, J=8Hz), 8.13 (1H, d, J=8Hz)

2) Methyl 2-(N-methylcarbamoyl)-1H-benzimidazole-4-carboxylate

NMR (CDCl<sub>3</sub>, δ) : 3.08 (3H, d, J=5Hz), 4.03 (3H, s), 7.40 (1H, t, J=8Hz), 7.47 (1H, br s), 7.98 (1H, d, J=8Hz), 8.04 (1H, d, J=8Hz)

#### Preparation 25

2-(N-Methylamino)-3-nitrobenzoic acid hydrochloride (250 mg) in methanol (5 ml) was hydrogenated under medium pressure (3 atm.) at ambient temperature for 3 hours. The reaction mixture was filtered through a bed of celite and the filtrate was concentrated in vacuo. The crude 3-amino-2-(N-methylamino)benzoic acid hydrochloride was used without further purification.

NMR (CD<sub>3</sub>OD, δ) : 3.06 (3H, s), 7.23 (1H, d, J=8Hz), 7.32 (1H, t, J=8Hz), 7.59 (1H, d, J=8Hz)

Preparation 26

The following compound was obtained according to a similar manner to that of Example 13.

- 5            3-Methyl-3H-benzimidazole-4-carboxylic acid hydrochloride  
NMR (DMSO-d<sub>6</sub>, δ) : 4.07 (3H, s), 7.50 (1H, t, J=8Hz),  
7.88 (1H, d, J=8Hz), 8.00 (1H, d, J=8Hz), 9.02 (1H,  
s)

10        Preparation 27

The following compound was obtained by using 2-amino-3-hydroxybenzoic acid as a starting compound according to a similar manner to that of Example 13.

- 15            4-Benzoxazolecarboxylic acid  
NMR (DMSO-d<sub>6</sub>, δ) : 7.55 (1H, t, J=8Hz), 7.92 (1H, d,  
J=8Hz), 8.03 (1H, d, J=8Hz), 8.85 (1H, s)

Preparation 28

- 20            The following compound was obtained by using 3-amino-2-hydroxybenzoic acid as a starting compound according to a similar manner to that of Example 13.

- 7-Benzoxazolecarboxylic acid  
25            NMR (DMSO-d<sub>6</sub>, δ) : 7.51 (1H, t, J=8Hz), 7.96 (1H, d,  
J=8Hz), 8.07 (1H, d, J=8Hz), 8.88 (1H, s)

Preparation 29

- 30            The following compound was obtained according to a similar manner to that of Example 5.

- Benzyl 1-methylindole-7-carboxylate  
NMR (CDCl<sub>3</sub>, δ) : 3.83 (3H, s), 5.41 (2H, s), 6.53 (1H,  
d, J=3Hz), 7.01-7.11 (2H, m), 7.31-7.42 (3H, m),  
35            7.47-7.50 (2H, m), 7.70 (1H, d, J=8Hz), 7.77 (1H,

d, J=8Hz)

### Preparation 30

To a solution of benzyl indole-4-carboxylate (1.85 g)  
5 and N,N-dimethylaminopyridine (180 mg) in acetonitrile (10 ml) was added portionwise di-tert-butyl dicarbonate (1.61 g), and then the mixture was stirred at ambient temperature for 2 hours and stand overnight. The resulting mixture was concentrated in vacuo and the residue was diluted with ethyl  
10 acetate (30 ml). The organic layer was washed successively with 1N hydrochloric acid, saturated sodium bicarbonate aqueous solution and brine. The solution was dried over magnesium sulfate and concentrated in vacuo. The residue was purified by silica gel column chromatography (eluent;  
15 n-hexane:ethyl acetate = 10:1) to give benzyl 1-tert-butoxycarbonylindole-4-carboxylate (2.26 g).

NMR (CDCl<sub>3</sub>, δ) : 1.68 (9H, s), 5.42 (2H, s), 7.26 (1H,  
d, J=4Hz), 7.31-7.43 (4H, m), 7.47-7.51 (2H, m),  
7.69 (1H, d, J=4Hz), 8.02 (1H, d, J=8Hz), 8.40 (1H,  
20 d, J=9Hz)

### Preparation 31

To a solution of methyl 2-methyl-1H-benzimidazole-4-carboxylate (250 mg) in N,N-dimethylformamide (4 ml) were  
25 added potassium carbonate (363 mg) and n-propyl bromide at ambient temperature and the mixture was stirred at the same temperature for 2 days. The reaction mixture was poured into water and the aqueous solution was extracted with ethyl acetate. The organic layer was washed with water and brine  
30 and the solution was dried over magnesium sulfate. The solvent was evaporated in vacuo and the residue was chromatographed on silica gel eluting with a mixture of n-hexane and ethyl acetate (1:1-1:2-1:3-ethyl acetate only) to give methyl 2-methyl-1-propyl-1H-benzimidazole-4-  
35 carboxylate (173 mg) as an oil.

NMR (CDCl<sub>3</sub>, δ) : 0.97 (3H, t, J=7Hz), 1.84 (2H, m),  
2.69 (3H, s), 4.05 (3H, s), 4.11 (2H, t, J=7Hz),  
7.27 (1H, t, J=8Hz), 7.49 (1H, d, J=8Hz), 7.94 (1H,  
d, J=8Hz)

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### Preparation 32

The following compound was obtained according to a similar manner to that of Preparation 31.

10 Methyl 1-(4-methoxybenzyl)-2-(N-methylcarbamoyl)-1H-benzimidazole-4-carboxylate

NMR (CDCl<sub>3</sub>, δ) : 3.04 (3H, d, J=5Hz), 3.74 (3H, s),  
4.04 (3H, s), 6.01 (2H, s), 6.80 (2H, d, J=8Hz),  
7.17 (2H, d, J=8Hz), 7.38 (1H, t, J=8Hz), 7.63 (1H,  
15 d, J=8Hz), 8.01 (1H, d, J=8Hz), 8.05 (1H, br peak)

### Example 1

To a mixture of 1H-imidazo[4,5-b]pyridine-7-carboxylic acid (203 mg) and oxalyl chloride (0.217 ml) in  
20 dichloromethane (25 ml) was added 1 drop of  
N,N-dimethylformamide and the mixture was stirred at ambient temperature for 2 hours. After being removed a solvent by evaporation, residual acid chloride in dichloromethane (5 ml) was added to a mixture of 4-amino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-ylcarbonyl)pent-1-yloxy]-phenyl]benzamide (400 mg) and triethylamine (210 mg) in  
25 dichloromethane (20 ml) and the mixture was stirred at ambient temperature for 2 hours. The mixture was washed successively with saturated aqueous sodium hydrogen carbonate and brine, and dried over sodium sulfate. The solvent was  
30 removed by rotary evaporation and the residue was purified by silica gel column chromatography (SiO<sub>2</sub> 30 g, 3% methanol in dichloromethane) to give 4-[1H-imidazo[4,5-b]pyridin-7-yl]-carbonylamino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonyl]pent-1-yloxy]phenyl]-  
35

benzamide (393 mg).

NMR (CDCl<sub>3</sub>, δ) : 1.42-1.61 (2H, m), 1.63-1.92 (4H, m),  
2.25 (3H, s), 2.29 (3H, s), 2.32-2.47 (6H, m), 3.34  
(3H, s), 3.42-3.55 (2H, m), 3.60-3.70 (2H, m),  
5 3.72-4.00 (5H, m), 6.50-6.66 (3H, m), 6.76-7.08  
(3H, m), 8.03 (1H, m), 8.32 (1H, s), 8.44 (1H, m),  
8.59 (1H, m)

### Example 2

10 The following compounds were obtained according to a  
similar manner to that of Example 1.

1) 4-[[1-(4-Toluenesulfonyl)indol-4-yl]carbonyl]amino-3-  
methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-  
15 yl)carbonylpent-1-yloxy]phenyl]benzamide

NMR (CDCl<sub>3</sub>, δ) : 1.48-1.58 (2H, m), 1.66-1.87 (4H, m),  
2.27 (3H, s), 2.31-2.39 (8H, m), 2.42-2.53 (4H, m),  
3.32 (3H, s), 3.52-3.58 (2H, m), 3.64-3.72 (2H, m),  
3.77 (3H, s), 3.83-4.00 (2H, m), 6.59 (1H, d,  
20 J=8Hz), 6.62 (1H, s), 6.85 (1H, d, J=8Hz), 6.92  
(1H, d, J=8Hz), 7.01 (1H, s), 7.19-7.27 (3H, m),  
7.38 (1H, t, J=8Hz), 7.58 (1H, d, J=8Hz), 7.69 (1H,  
d, J=4Hz), 7.75 (2H, d, J=8Hz), 8.17 (1H, d,  
J=8Hz), 8.28 (1H, d, J=8Hz), 8.47 (1H, s)

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2) 4-[(1-Pivaloyloxymethylindol-7-yl)carbonyl]amino-3-  
methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-  
yl)carbonylpent-1-yloxy]phenyl]benzamide

NMR (CDCl<sub>3</sub>, δ) : 0.84 (9H, s), 1.48-1.61 (2H, m),  
30 1.68-1.90 (4H, m), 2.28 (3H, s), 2.31 (3H, s),  
2.33-2.46 (6H, m), 3.33 (3H, s), 3.48-3.54 (2H, m),  
3.60-3.68 (2H, m), 3.70 (3H, s), 3.88-4.00 (2H, m),  
6.28 (2H, s), 6.57 (1H, d, J=3Hz), 6.59-6.66 (2H,  
m), 6.83 (1H, d, J=8Hz), 6.97 (1H, d, J=8Hz), 7.02  
35 (1H, s), 7.19 (1H, t, J=8Hz), 7.29 (1H, d, J=3Hz),



7.42 (1H, d, J=8Hz), 7.74 (1H, d, J=8Hz), 8.28-8.37 (2H, m)

- 3) 4-[(1-Methylindol-7-yl)carbonyl]amino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide

NMR (CDCl<sub>3</sub>, δ) : 1.48-1.89 (6H, m), 2.29 (6H, s), 2.31-2.42 (6H, m), 3.33 (3H, s), 3.46-3.51 (2H, m), 3.59-3.67 (2H, m), 3.72 (3H, s), 3.80 (3H, s), 3.88-4.00 (2H, m), 6.55 (1H, d, J=4Hz), 6.61 (1H, d, J=8Hz), 6.67 (1H, s), 6.81-7.12 (5H, m), 7.33 (1H, d, J=8Hz), 7.72 (1H, d, J=8Hz), 8.28-8.36 (2H, m)

- 4) 4-(1-tert-Butoxycarbonyl-2-ethoxycarbonylindol-4-yl)carbonyl]amino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide

NMR (CDCl<sub>3</sub>, δ) : 1.40 (3H, t, J=8Hz), 1.50-1.89 (6H, m), 1.63 (9H, s), 2.28 (3H, s), 2.30 (3H, s), 2.32-2.43 (6H, m), 3.34 (3H, s), 3.47-3.52 (2H, m), 3.60-3.68 (2H, m), 3.79 (3H, s), 3.87-4.00 (2H, m), 4.38 (2H, q, J=8Hz), 6.60 (1H, d, J=8Hz), 6.64 (1H, s), 6.86 (1H, d, J=8Hz), 6.95 (1H, d, J=8Hz), 7.06 (1H, s), 7.48 (1H, t, J=8Hz), 7.62 (1H, d, J=8Hz), 7.69 (1H, s), 8.27-8.33 (2H, m), 8.54 (1H, s)

- 5) 4-[2-Chloro-1H-benzimidazol-4-yl]carbonylamino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide

NMR (CDCl<sub>3</sub>, δ) : 1.45-1.60 (2H, m), 1.63-1.92 (4H, m), 2.25 (3H, s), 2.29 (3H, s), 2.31-2.49 (6H, m), 3.35 (3H, s), 3.44-3.55 (2H, m), 3.59-3.70 (2H, m), 3.71-4.01 (5H, m), 6.52-6.66 (2H, m), 6.80-7.06 (3H, m), 7.24-7.37 (1H, m), 7.42-8.50 (3H, m)

6) 3-Methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]-4-(purin-6-yl)carbonyl-aminobenzamide

5 NMR (DMSO-d<sub>6</sub>, δ) : 1.40-1.50 (2H, m), 1.50-1.62 (2H, m), 1.70-1.79 (2H, m), 2.14 (3H, s), 2.18-2.36 (9H, m), 3.20 (3H, s), 3.35-3.43 (6H, m), 3.75 (3H, s), 3.81-3.99 (2H, m), 6.65 (1H, d, J=7Hz), 6.82 (1H, s), 6.95-7.08 (3H, m), 8.27 (1H, d, J=6Hz), 8.83 (1H, s), 9.10 (1H, s)

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7) 4-(3-Benzyl-2-methoxymethyl-3H-benzimidazol-4-yl)carbonylamino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide

15 NMR (CDCl<sub>3</sub>, δ) : 1.49-1.64 (2H, m), 1.64-1.81 (2H, m), 1.81-1.95 (2H, m), 2.21-2.31 (6H, m), 2.31-2.44 (6H, m), 3.34 (3H, s), 3.43 (3H, s), 3.46-3.54 (2H, m), 3.58 (3H, s), 3.60-3.70 (2H, m), 3.90-4.04 (2H, m), 4.82 (2H, s), 5.63 (2H, s), 6.60-6.75 (6H, m), 6.75-6.83 (1H, m), 6.83-6.93 (2H, m), 6.99 (1H, d, J=8Hz), 7.19-7.31 (2H, m), 7.55 (1H, s), 7.90 (1H, d, J=8Hz), 8.20 (1H, d, J=8Hz)

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8) 4-(1,2-Dimethyl-1H-benzimidazol-4-yl)carbonylamino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide

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30 NMR (CDCl<sub>3</sub>, δ) : 1.45-1.76 (4H, m), 1.76-1.91 (2H, m), 2.25 (3H, s), 2.30 (3H, s), 2.32-2.42 (6H, m), 2.69 (3H, s), 3.33 (3H, s), 3.45-3.52 (2H, m), 3.59-3.68 (2H, m), 3.78 (3H, s), 3.81-3.90 (4H, m), 3.90-4.01 (1H, m), 6.54-6.64 (2H, m), 6.86 (1H, d, J=8Hz), 6.96 (1H, d, J=8Hz), 7.01 (1H, s), 7.34 (1H, t, J=8Hz), 7.44 (1H, d, J=8Hz), 8.14 (1H, d, J=8Hz), 8.53 (1H, d, J=8Hz)

35 9) 4-(1-Ethyl-2-methyl-1H-benzimidazol-4-yl)carbonylamino-

3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide

NMR (CDCl<sub>3</sub>, δ) : 1.44 (3H, t, J=7Hz), 1.48-1.61 (2H, m), 1.65-1.75 (2H, m), 1.75-1.98 (2H, m), 2.27 (3H, s), 2.29 (3H, s), 2.31-2.43 (6H, m), 2.70 (3H, s), 3.34 (3H, s), 3.44-3.53 (2H, m), 3.59-3.68 (2H, m), 3.79-3.90 (4H, m), 3.90-4.00 (1H, m), 4.22 (2H, q, J=7Hz), 6.53-6.63 (2H, m), 6.86 (1H, d, J=8Hz), 6.96 (1H, d, J=8Hz), 7.01 (1H, s), 7.34 (1H, t, J=8Hz), 7.46 (1H, d, J=8Hz), 8.13 (1H, d, J=8Hz), 8.52 (1H, d, J=8Hz)

10) 3-Methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]-4-(2-methyl-1-propyl-1H-benzimidazol-4-yl)carbonylaminobenzamide

NMR (CDCl<sub>3</sub>, δ) : 0.97 (3H, t, J=7Hz), 1.44-1.74 (4H, m), 1.74-1.92 (4H, m), 2.24 (3H, s), 2.27 (3H, s), 2.31-2.42 (6H, m), 2.67 (3H, s), 3.32 (3H, s), 3.43-3.53 (2H, m), 3.58-3.66 (2H, m), 3.76-3.90 (4H, m), 3.90-4.00 (1H, m), 4.13 (2H, t, J=7Hz), 6.52-6.62 (2H, m), 6.86 (1H, d, J=8Hz), 6.96 (1H, d, J=8Hz), 7.00 (1H, s-like), 7.33 (1H, t, J=8Hz), 7.45 (1H, d, J=8Hz), 8.13 (1H, d, J=8Hz), 8.53 (1H, d, J=8Hz)

11) 3-Methoxy-4-[1-(4-methoxybenzyl)-2-(N-methylcarbamoyl)-1H-benzimidazol-4-yl]carbonylamino-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide

NMR (CDCl<sub>3</sub>, δ) : 1.46-1.63 (2H, m), 1.63-1.77 (2H, m), 1.77-1.91 (2H, m), 2.25 (3H, s), 2.28 (3H, s), 2.31-2.41 (6H, m), 3.13 (3H, d, J=5Hz), 3.34 (3H, s), 3.44-3.51 (2H, m), 3.56-3.65 (2H, m), 3.74 (3H, s), 3.82-4.01 (5H, m), 6.00 (2H, s), 6.58 (1H, d, J=8Hz), 6.64 (1H, s), 6.82 (2H, d, J=8Hz), 6.87 (1H, d, J=8Hz), 6.97 (1H, d, J=8Hz), 7.10 (1H, s),

7.21 (2H, d, J=8Hz), 7.46 (1H, t, J=8Hz), 7.60 (1H, d, J=8Hz), 7.95 (1H, br peak), 8.24 (1H, d, J=8Hz), 8.50 (1H, d, J=8Hz)

- 5 12) 4-(2-tert-Butyldiphenylsiloxymethyl-1H-benzimidazol-4-yl)carbonylamino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide

10 NMR (DMSO-d<sub>6</sub>, δ) : 1.04 (9H, s), 1.35-1.49 (2H, m), 1.49-1.64 (2H, m), 1.64-1.80 (2H, m), 2.11 (3H, s), 2.13-2.25 (7H, m), 2.30 (2H, t, J=7.5Hz), 3.17 (3H, s), 3.27-3.45 (7H, m), 3.84 (1H, br peak), 3.96 (1H, br peak), 5.03 (2H, s), 6.63 (1H, d, J=8Hz), 6.80 (2H, s-like), 6.94 (1H, d, J=8Hz), 7.02 (1H, d, J=8Hz), 7.30-7.50 (7H, m), 7.69 (4H, d, J=8Hz), 7.79 (1H, d, J=8Hz), 7.91 (1H, d, J=8Hz), 8.35 (1H, d, J=8Hz)

- 13) 4-(Benzoxazol-4-yl)carbonylamino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide

20 NMR (CDCl<sub>3</sub>, δ) : 1.47-1.65 (2H, m), 1.65-1.78 (2H, m), 1.78-1.92 (2H, m), 2.26 (3H, s), 2.30 (3H, s), 2.32-2.43 (6H, m), 3.35 (3H, s), 3.44-3.54 (2H, m), 3.58-3.68 (2H, m), 3.79-4.02 (5H, m), 6.54-6.66 (2H, m), 6.87 (1H, d, J=8Hz), 6.98 (1H, d, J=8Hz), 7.04 (1H, s-like), 7.55 (1H, t, J=8Hz), 7.77 (1H, d, J=8Hz), 8.23-8.31 (2H, m), 8.44 (1H, d, J=8Hz)

- 14) 4-(Benzoxazol-7-yl)carbonylamino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide

30 NMR (CDCl<sub>3</sub>, δ) : 1.45-1.76 (4H, m), 1.76-1.90 (2H, m), 3.33 (3H, s), 3.43-3.52 (2H, m), 3.56-3.68 (2H, m), 3.83 (3H, s), 3.86-4.01 (2H, m), 6.54-6.65 (2H, m), 6.85 (1H, d, J=8Hz), 6.96 (1H, d, J=8Hz), 7.06 (1H,

s), 7.52 (1H, t, J=8Hz), 7.97 (1H, d, J=8Hz), 8.18 (1H, d, J=8Hz), 8.23 (1H, s), 8.36 (1H, d, J=8Hz), 9.50 (1H, s)

- 5 15) 4-(3-Bromo-2-methylimidazo[1,2-a]pyridin-8-yl)carbonylamino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide

10 NMR (CDCl<sub>3</sub>, δ) : 1.44-1.61 (2H, m), 1.61-1.78 (2H, m), 1.78-1.92 (2H, m), 2.28 (3H, s), 2.30 (3H, s), 2.33-2.45 (3H, m), 2.54 (3H, s), 3.33 (3H, s), 3.45-3.55 (2H, m), 3.60-3.70 (2H, m), 3.88 (3H, s), 3.91-4.01 (2H, m), 6.53-6.64 (2H, m), 6.86 (1H, d, J=8Hz), 6.93-7.03 (2H, m), 7.07 (1H, t, J=8Hz), 8.19 (1H, d, J=8Hz), 8.25 (1H, d, J=8Hz), 8.45 (1H, d, J=8Hz)

- 16) 3-Methoxy-N-methyl-4-(2-methylimidazo[1,2-a]pyridin-4-yl)carbonylamino-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide

20 NMR (CDCl<sub>3</sub>, δ) : 1.45-1.65 (2H, m), 1.65-1.75 (2H, m), 1.75-1.90 (2H, m), 2.25 (3H, s), 2.29 (3H, s), 2.31-2.42 (6H, m), 2.52 (3H, s), 3.33 (3H, s), 3.42-3.52 (2H, m), 3.57-3.66 (2H, m), 3.77-3.90 (4H, m), 3.90-4.02 (1H, m), 6.51-6.62 (2H, m), 6.80-7.04 (4H, m), 7.41 (1H, s), 8.16 (2H, d-like), 8.48 (1H, d, J=8Hz)

### Example 3

To a suspension of 3-methyl-3H-benzimidazole-4-carboxylic acid hydrochloride (112 mg) in dichloromethane (2 ml) was added oxalyl chloride (79 mg) in an ice water bath under nitrogen and then added 1 drop of N,N-dimethylformamide. After being stirred under the same condition for 2 hours, the reaction mixture was concentrated in vacuo. The residue was added to a solution of 4-amino-3-methoxy-N-

methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide (150 mg) in pyridine (2 ml) under nitrogen at ambient temperature and the mixture was stirred for 2 hours and allowed to stand at same temperature  
5 overnight. The reaction mixture was concentrated in vacuo and the residue was dissolved in chloroform. The solution was washed with water and saturated aqueous sodium bicarbonate solution and the organic layer was dried over magnesium sulfate. The solvent was evaporated in vacuo and  
10 the residue was purified by preparative thin-layer chromatography (ethyl acetate-methanol = 1:1) to give 3-methoxy-N-methyl-4-(3-methyl-3H-benzimidazol-4-yl)carbonylamino-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)-carbonylpent-1-yloxy]phenyl]benzamide (52 mg) as a powder.  
15 NMR (CDCl<sub>3</sub>, δ) : 1.45-1.63 (2H, m), 1.63-1.79 (2H, m), 1.79-1.91 (2H, m), 2.30 (6H, s), 2.32-2.43 (6H, m), 3.33 (3H, s), 3.43-3.52 (2H, m), 3.52-3.68 (2H, m), 3.75 (3H, s), 3.83-4.03 (5H, m), 6.55-6.72 (2H, m), 6.88 (1H, d, J=8Hz), 6.97 (1H, d, J=8Hz), 7.04 (1H, s), 7.22-7.35 (1H, m), 7.50 (1H, d, J=8Hz), 7.88 (1H, s), 7.95 (1H, d, J=8Hz), 8.30 (1H, d, J=6Hz),  
20 8.38 (1H, s)

#### Example 4

25 To a solution of 4-amino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]-benzamide (6.0 g) in 1,4-dioxane (200 ml) was added 8-nitro-2-trifluoromethyl-3,1-benzoxazin-4-one (3.24 g) and the mixture was stirred at 100°C for 4 hours. To the mixture was  
30 added 8-nitro-2-trifluoromethyl-3,1-benzoxazin-4-one (3.24 g) and the solution was stirred at 100°C for additional 3 hours. To the mixture was added 1N sodium hydroxide solution (90 ml) and the resulting solution was stirred at 60°C for 1 hour. After being concentrated in vacuo, the residue was diluted  
35 with chloroform and the organic solution was washed with

saturated aqueous sodium bicarbonate solution and brine. The organic layer was dried over magnesium sulfate and the solvent was concentrated in vacuo to give 3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]-4-(3-nitro-2-trifluoroacetylaminobenzoyl)-aminobenzamide as a yellow powder (10.6 g). The crude product was used for next step without further purification.

#### Example 5

To a solution of 4-[(indol-4-yl)carbonyl]amino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide (160 mg) in N,N-dimethylformamide (3.0 ml) was added portionwise potassium tert-butoxide (37.3 mg) at 0°C and the mixture was stirred at 0°C for 1 hour. Methyl iodide (47.2 mg) was added to the mixture and the solution was stirred at 0°C for 1 hour. The reaction was quenched with water and then the aqueous solution was extracted with ethyl acetate. Drying, filtering and removal of solvents afforded a crude product. The crude product was purified by column chromatography (eluent; 2% methanol in chloroform) to give 4-[(1-methylindol-4-yl)-carbonyl]amino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide (65 mg) as a white syrup.

NMR (CDCl<sub>3</sub>, δ) : 1.49-1.89 (6H, m), 2.28 (3H, s), 2.29 (3H, s), 2.32-2.42 (6H, m), 3.34 (3H, s), 3.46-3.52 (2H, m), 3.60-3.68 (2H, m), 3.78 (3H, s), 3.86 (3H, s), 3.88-3.99 (2H, m), 6.60 (1H, d, J=8Hz), 6.64 (1H, s), 6.87 (1H, d, J=8Hz), 6.91-6.98 (2H, m), 7.06 (1H, s), 7.21 (1H, d, J=3Hz), 7.27-7.32 (1H, m), 7.49 (1H, d, J=8Hz), 7.63 (1H, d, J=8Hz), 8.38 (1H, d, J=8Hz), 8.76 (1H, s)

#### Example 6

The following compound was obtained according to a

similar manner to that of Example 5.

4-[(1-Isopropylindol-4-yl)carbonyl]amino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide

NMR (CDCl<sub>3</sub>, δ) : 1.48-1.59 (2H, m), 1.57 (6H, d, J=7Hz), 1.66-1.88 (4H, m), 2.29 (6H, s), 2.32-2.40 (6H, m), 3.33 (3H, s), 3.46-3.51 (2H, m), 3.60-3.67 (2H, m), 3.79 (3H, s), 3.88-4.00 (2H, m), 4.68-4.78 (1H, m), 6.60 (1H, d, J=8Hz), 6.65 (1H, s), 6.87 (1H, d, J=8Hz), 6.93 (1H, d, J=8Hz), 6.97 (1H, d, J=3Hz), 7.07 (1H, s), 7.27 (1H, t, J=8Hz), 7.38 (1H, d, J=3Hz), 7.54 (1H, d, J=8Hz), 7.62 (1H, d, J=8Hz), 8.38 (1H, d, J=8Hz), 8.76 (1H, s)

#### Example 7

To a solution of 4-(2-amino-3-nitrobenzoyl)amino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide (3.88 g) in ethanol (40 ml) were added a solution of ammonium chloride (385 mg) in water (10 ml) and iron powder (2.01 g) and the mixture was stirred at 100°C for 2 hours. The mixture was filtered through a bed of celite and the filtrate was concentrated in vacuo. The residue was diluted with ethyl acetate and the solution was washed with aqueous saturated sodium bicarbonate solution and brine. The organic layer was dried over magnesium sulfate and the solution was concentrated in vacuo to give 4-(2,3-diaminobenzoyl)amino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide as a yellow powder (3.42 g).

NMR (CDCl<sub>3</sub>, δ) : 1.47-1.59 (2H, m), 1.59-1.90 (4H, m), 2.29 (3H, s), 2.30 (3H, s), 2.33-2.42 (6H, m), 3.33 (3H, s), 3.47-3.50 (2H, m), 3.62-3.67 (2H, m), 3.77 (3H, s), 3.82-4.00 (2H, m), 6.57-6.68 (3H, m), 6.80-7.03 (5H, m), 8.20 (1H, d, J=7Hz), 8.44 (1H,



s)

Example 8

To a suspension of 4-(2,3-diaminobenzoyl)amino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide (200 mg) in water (5 ml) was added 1N hydrochloric acid (1.3 ml) and then dicyandiamide (545 mg) was added to the stirred reaction mixture. The solution was heated under reflux for 24 hours. After cooling, aqueous sodium hydrogen carbonate was added to the mixture and extracted with ethyl acetate. The extract was washed with brine and dried over sodium sulfate. After evaporation of the solvent, the residue was purified by silica gel column chromatography (SiO<sub>2</sub>, 30 g, 15% methanol in chloroform) to give 4-[2-guanidinobenzimidazol-4-yl]carbonylamino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide (100 mg) as yellow amorphous.

NMR (CDCl<sub>3</sub>,  $\delta$ ) : 1.36-1.83 (6H, m), 2.25 (3H, s), 2.30 (3H, s), 2.32-2.48 (6H, m), 3.34 (3H, s), 3.43-3.74 (5H, m), 3.78 (3H, s), 3.82-3.98 (1H, m), 6.56 (1H, s), 6.68 (1H, d, J=8Hz), 6.94 (1H, d, J=8Hz), 7.02 (1H, d, J=8Hz), 7.08-7.18 (2H, m), 7.36 (1H, d, J=8Hz), 7.97 (1H, d, J=8Hz), 8.44 (1H, d, J=8Hz)

Example 9

To a solution of 4-(2,3-diaminobenzoyl)amino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide (110 mg) in anhydrous tetrahydrofuran (2 ml) was added 1,1'-thiocarbonyldiimidazole (48 mg) under nitrogen at ambient temperature and stirred at same temperature for 1 day. After being concentrated in vacuo, the residue was diluted with a mixture of chloroform and saturated sodium bicarbonate aqueous solution and the organic layer was separated. The

organic layer was washed with water and brine and the solution was dried over magnesium sulfate. The solvent was evaporated in vacuo and the residue was purified by preparative thin-layer chromatography (ethyl acetate-methanol = 1:1) to give 4-(2-mercapto-1H-benzimidazol-4-yl)carbonylamino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide (96 mg) as a powder.

NMR (CDCl<sub>3</sub>, δ) : 1.48-1.62 (2H, m), 1.66-1.78 (2H, m),  
1.78-1.90 (2H, m), 2.28 (3H, s), 2.31 (3H, s),  
2.33-2.46 (6H, m), 3.33 (3H, s), 3.45-3.53 (2H, m),  
3.60-3.70 (2H, m), 3.81 (3H, s), 3.84-4.01 (2H, m),  
6.55-6.67 (2H, m), 6.86 (1H, d, J=8Hz), 6.94 (1H, d, J=8Hz), 7.03 (1H, s), 7.12 (2H, s-like), 7.17-7.40 (2H, m), 7.70 (1H, s), 8.20 (1H, d, J=8Hz), 8.65 (1H, s)

#### Example 10

To a suspension of 4-(2,3-diaminobenzoyl)amino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide (242 mg) in water (3 ml) was added cyanogen bromide (46 mg) at ambient temperature. The mixture was stirred at the same temperature for 2 hours and then allowed to stand at the same temperature overnight. To the reaction mixture was added saturated aqueous sodium bicarbonate solution and the solution was extracted with chloroform. The organic layer was washed with water, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by preparative thin-layer chromatography (chloroform-methanol = 10:1) to give 4-(2-amino-1H-benzimidazol-4-yl)carbonylamino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide (67 mg) as a powder.

NMR (CDCl<sub>3</sub>, δ) : 1.40-1.56 (2H, m), 1.56-1.87 (4H, m),  
2.23 (3H, s), 2.26 (3H, s), 2.30-2.44 (6H, m), 3.33

(3H, s), 3.41-3.53 (2H, m), 3.53-3.69 (5H, m),  
3.69-3.83 (1H, m), 3.83-4.00 (1H, m), 5.54 (2H, br  
peak), 6.50-6.66 (2H, m), 6.80-6.95 (2H, m), 6.95-  
7.10 (2H, m), 7.69 (1H, d-like), 8.37 (1H, d-like)

5

Example 11

To 4-(2,3-diaminobenzoyl)amino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide (120 mg) were added acetic acid (47  
10 mg) and water (0.5 ml) and the suspension was stirred at ambient temperature until a clear solution was obtained. After being cooled to 5°C a cold solution of sodium nitrite (15 mg) in water (0.3 ml) was added all at once to the  
15 solution. The reaction mixture was stirred at 5°C for 5 minutes and then the temperature was raised to 75°C and stirred for 10 minutes. The reaction mixture was cooled to 20°C and the solution was stirred in an ice water bath for 1 hour. To the reaction mixture were added saturated aqueous sodium bicarbonate solution and chloroform and the organic  
20 layer was separated. The organic layer was washed with saturated aqueous sodium bicarbonate solution and brine and dried over magnesium sulfate. The solvent was evaporated and the residue was purified by preparative thin-layer chromatography (chloroform-methanol = 10:1) to give 4-(1H-benzotriazol-4-yl)carbonylamino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide (81 mg) to give a powder.

NMR (CDCl<sub>3</sub>, δ) : 1.46-1.62 (2H, m), 1.65-1.76 (2H, m),  
1.76-1.90 (2H, m), 2.26 (3H, s), 2.32-2.45 (7H, m),  
30 2.45-2.59 (2H, m), 3.35 (3H, s), 3.50-3.66 (3H, m), 3.73-3.89 (5H, m), 3.89-3.99 (1H, m), 6.57-6.65 (2H, m), 6.93 (1H, d, J=8Hz), 6.99-7.05 (2H, m), 7.53 (1H, t, J=8Hz), 8.00 (1H, d, J=8Hz), 8.10 (1H, d, J=8Hz), 8.34 (1H, d, J=8Hz), 10.04 (1H, s)

35

Example 12

To a stirred solution of 4-(2,3-diaminobenzoyl)amino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide (145 mg) in a mixture of acetonitrile and benzene [1:4(v/v)] was added methoxycarbonyl isothiocyanate (36 mg) and the reaction mixture was stirred at ambient temperature for 5 minutes. After being added 1,3-dicyclohexylcarbodiimide (73 mg) to the solution, the resulting mixture was stirred at reflux temperature for 5 hours. The reaction mixture was concentrated in vacuo and the residue was dissolved in chloroform. The solution was washed with saturated aqueous sodium bicarbonate solution, water and brine, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by chromatography on silica gel (chromatorex) eluting with chloroform and preparative thin-layer chromatography (chloroform-methanol = 10:1) to give 3-methoxy-4-(2-methoxycarbonylamino-1H-benzimidazol-4-yl)carbonylamino-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide (82 mg) as a powder.

NMR (DMSO-d<sub>6</sub>, δ) : 1.36-1.49 (2H, m), 1.49-1.62 (2H, m), 1.67-1.83 (2H, m), 2.13 (3H, s), 2.15-2.38 (9H, m), 3.20 (3H, s), 3.36-3.45 (4H, m), 3.74 (3H, s), 3.79-3.90 (4H, m), 3.90-4.03 (1H, m), 6.65 (1H, d, J=8Hz), 6.82 (1H, s), 6.89 (1H, s), 6.93 (1H, d, J=8Hz), 7.03 (1H, d, J=8Hz), 7.20 (1H, t J=8Hz), 7.67 (1H, d, J=8Hz), 7.82 (1H, d, J=8Hz), 8.21-8.28 (1H, m)

Example 13

A mixture of 4-(2,3-diaminobenzoyl)amino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide (90 mg) and trimethyl orthoformate (1 ml) was refluxed for 4 hours. After removing excess

reagent by evaporation, the residue was dissolved in chloroform and the solution was washed with water and saturated aqueous sodium bicarbonate solution. The organic layer was dried over magnesium sulfate and the solvent was evaporated in vacuo. The residue was purified by preparative thin-layer chromatography (chloroform-methanol = 10:1) to give 4-(1H-benzimidazol-4-yl)carbonylamino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide (51 mg) as a powder.

10 NMR (CDCl<sub>3</sub>,  $\delta$ ) : 1.48-1.62 (2H, m), 1.67-1.78 (2H, m),  
1.78-1.91 (2H, m), 2.21-2.31 (6H, m), 2.31-2.43  
(6H, m), 3.35 (3H, s), 3.45-3.56 (2H, m), 3.60-3.69  
(2H, m), 3.81 (1H, d-like), 3.81-3.90 (1H, m),  
3.90-4.01 (1H, m), 6.54-6.65 (2H, m), 6.84-6.93  
15 (1H, m), 6.93-7.07 (2H, m), 7.31-7.50 (1H, m), 7.59  
(1H x 1/2, d, J=8Hz), 7.68 (1H x 1/2, d, J=8Hz),  
7.98-8.33 (2H, m), 8.45-8.56 (1H x 1/2, m), 8.79  
(1H x 1/2, s)

#### 20 Example 14

To a solution of 4-(2,3-diaminobenzoyl)amino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide (200 mg) in acetic acid (1 ml) was added tetramethyl orthocarbonate (66 mg) at ambient temperature and the solution was allowed to stand at the same temperature for 3 days. After being concentrated in vacuo, the residue was diluted with chloroform and saturated sodium bicarbonate aqueous solution. The organic layer was separated and washed with water and brine. The solution was dried over magnesium sulfate and the solvent was evaporated in vacuo. The residue was purified by preparative thin-layer chromatography (chloroform-methanol = 10:1) to give 4-(2-methoxy-1H-benzimidazol-4-yl)carbonylamino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide (171 mg) as a powder.

NMR (CDCl<sub>3</sub>, δ) : 1.44-1.65 (2H, m), 1.65-1.76 (2H, m),  
1.76-1.90 (2H, m), 2.27 (3H, s), 2.29 (3H, s),  
2.33-2.45 (6H, m), 3.34 (3H, s), 3.42-3.54 (2H, m),  
3.58-3.68 (2H, m), 3.71 (3H x 2/3, s), 3.80 (3H x  
5 1/3, s), 3.82-4.02 (2H, m), 4.20 (3H x 1/3, s),  
4.28 (3H x 2/3, s), 6.53-6.68 (2H, m), 6.81-7.08  
(3H, m), 7.17-7.43 (3H, m), 7.70 (1H x 1/3, d,  
J=8Hz), 8.06 (1H x 2/3, d, J=8Hz), 8.22-8.31 (1H x  
10 1/3, m), 8.54 (1H x 2/3, d, J=8Hz), 8.72 (1H x 1/3,  
s), 8.90 (1H x 2/3, s)

### Example 15

The following compounds were obtained according to a  
similar manner to that of Example 14.

15 1) 4-(2-Ethoxy-1H-benzimidazol-4-yl)carbonylamino-3-  
methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-  
yl)carbonylpent-1-yloxy]phenyl]benzamide

20 NMR (CDCl<sub>3</sub>, δ) : 1.44-1.65 (5H, m), 1.65-1.76 (2H, m),  
1.76-1.90 (2H, m), 2.25 (3H, s), 2.29 (3H, s),  
2.31-2.43 (6H, m), 3.33 (3H, s), 3.44-3.53 (2H, m),  
3.60-3.68 (2H, m), 3.74 (3H x 3/4, s), 3.80 (3H x  
1/4, s), 3.83-4.01 (2H, m), 4.61 (2H x 1/4, q,  
J=7.5Hz), 4.73 (2H x 3/4, q, J=7.5Hz), 6.55-6.66  
25 (2H, m), 6.81-6.99 (2H, m), 7.02 (1H, s), 7.20 (1H,  
t, J=8Hz), 7.35 (1H, d, J=8Hz), 7.67 (1H x 1/4, d,  
J=8Hz), 8.05 (1H x 3/4, d, J=8Hz), 8.26 (1H x 1/4,  
d, J=8Hz), 8.54 (1H x 3/4, d, J=8Hz), 8.70-8.78  
(1H, m)

30 2) 3-Methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-  
1-yl)carbonylpent-1-yloxy]phenyl]-4-(2-propoxy-1H-  
benzimidazol-4-yl)carbonylaminobenzamide

35 NMR (CD<sub>3</sub>OD, δ) : 1.06 (3H, t, J=7.5Hz), 1.42-1.56 (2H,  
m), 1.56-1.71 (2H, m), 1.71-1.96 (4H, m), 2.20 (3H,

s), 2.25 (3H, s), 2.28-2.97 (6H, m), 3.29 (3H, s),  
3.40-3.62 (4H, m), 3.70 (3H, s), 3.79-4.01 (2H, m),  
4.56 (2H, t, J=7Hz), 6.67 (1H, d, J=8Hz), 6.76 (1H,  
s), 6.94 (1H, s), 6.96-7.05 (2H, m), 7.13 (1H, t,  
J=8Hz), 7.35 (1H, d, J=8Hz), 7.82 (1H, d, J=8Hz),  
8.40 (1H, d, J=8Hz)

#### Example 16

A suspension of 4-(2,3-diaminobenzoyl)amino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide (100 mg) in acetic acid (1 ml) was refluxed for 8 hours. After being evaporated in vacuo, the residue was dissolved chloroform and the solution was washed with water and saturated aqueous sodium bicarbonate solution. The organic layer was dried over magnesium sulfate and the solvent was evaporated in vacuo. The residue was purified by preparative thin-layer chromatography (chloroform-methanol = 10:1) to give 3-methoxy-N-methyl-4-(2-methyl-1H-benzimidazol-4-yl)carbonylamino-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)-carbonylpent-1-yloxy]phenyl]benzamide (84 mg) as a powder.

NMR (CDCl<sub>3</sub>, δ) : 1.43-1.60 (2H, m), 1.60-1.75 (2H, m),  
1.75-1.89 (2H, m), 2.25 (3H, s), 2.29 (3H, s),  
2.31-2.43 (6H, m), 2.63 (3H, s), 3.33 (3H, s),  
3.43-3.53 (2H, m), 3.58-3.68 (2H, m), 3.73-3.90  
(4H, m), 3.90-4.00 (1H, m), 6.53-6.64 (2H, m),  
6.82-6.91 (1H, m), 6.91-7.05 (2H, m), 7.22-7.33 (1H  
x 2/3, m), 7.43-7.53 (1H, m), 7.80-7.90 (1H x 1/3,  
m), 8.11 (1H x 2/3, d, J=8Hz), 8.23-8.31 (1H x 1/3,  
m), 8.47-8.57 (1H x 2/3, m), 8.75 (1H x 1/3, s),  
9.83 (1H x 2/3, s), 10.67 (1H x 1/3, s)

#### Example 17

The following compounds were obtained according to a similar manner to that of Example 16.

1) 3-Methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]-4-(2-trifluoromethyl-1H-benzimidazol-4-yl)carbonylamino benzamide

5 NMR (CDCl<sub>3</sub>, δ) : 1.43-1.62 (2H, m), 1.62-1.77 (2H, m),  
1.77-1.94 (2H, m), 3.35 (3H, s), 3.43-3.58 (2H, m),  
3.58-3.70 (2H, m), 3.80 (3H, s), 3.82-3.91 (1H, m),  
3.91-4.01 (1H, m), 6.53-6.66 (2H, m), 6.90 (1H, d,  
J=8Hz), 6.94-7.04 (2H, m), 7.48 (1H, t, J=8Hz),  
7.78 (1H, br peak), 8.08 (1H, br peak), 8.41 (1H,  
10 br peak)

2) 4-(2-Ethyl-1H-benzimidazol-4-yl)carbonylamino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)-carbonylpent-1-yloxy]phenyl]benzamide

15 NMR (CDCl<sub>3</sub>, δ) : 1.41-1.75 (7H, m), 1.75-1.90 (2H, m),  
2.23-2.31 (6H, m), 2.31-2.42 (6H, m), 2.99 (2H, q,  
J=7.5Hz), 3.34 (3H, m), 3.44-3.52 (2H, m), 3.59-  
3.67 (2H, m), 3.76-3.90 (4H, m), 3.90-4.00 (1H, m),  
6.53-6.64 (2H, m), 6.83-7.04 (3H, m), 7.24-7.34  
20 (1H, m), 7.44-7.55 (1H, m), 7.89 (1H x 1/3, d,  
J=8Hz), 8.14 (1H x 2/3, d, J=8Hz), 8.28 (1H x 1/3,  
d, J=8Hz), 8.37 (1H x 2/3, d, J=8Hz), 8.78 (1H x  
1/3, s), 9.56 (1H x 2/3, s), 10.75 (1H x 1/3, s)

25 3) 3-Methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]-4-(2-n-propyl-1H-benzimidazol-4-yl)carbonylamino benzamide

NMR (CD<sub>3</sub>OD, δ) : 1.06 (3H, t, J=7.5Hz), 1.47-1.60 (2H,  
m), 1.60-1.74 (2H, m), 1.74-1.90 (2H, m), 1.90-2.05  
30 (2H, m), 2.23 (3H, s), 2.28 (3H, s), 2.31-2.47 (6H,  
m), 2.95 (2H, t, J=7.5Hz), 3.30 (3H, s), 3.48-3.61  
(4H, m), 3.79 (3H, s), 3.84-3.94 (1H, m), 3.94-4.06  
(1H, m), 6.70 (1H, d, J=8Hz), 6.79 (1H, s), 6.97  
(1H, s), 6.99-7.08 (2H, m), 7.30 (1H, t, J=8Hz),  
35 7.94 (1H, d, J=8Hz), 8.40 (1H, d, J=8Hz)



4) 4-(2-Isopropyl-1H-benzimidazol-4-yl)carbonylamino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide

NMR (CDCl<sub>3</sub>, δ) : 1.43-1.59 (8H, m), 1.59-1.75 (2H, m),  
5 1.75-1.90 (2H, m), 2.22-2.30 (6H, m), 2.30-2.42  
(6H, m), 3.18-3.30 (1H, m), 3.33 (3H, s), 3.43-3.51  
(2H, m), 3.60-3.67 (2H, m), 3.75-3.89 (4H, m),  
3.89-4.01 (1H, m), 6.53-6.65 (2H, m), 6.87 (1H, d,  
J=8Hz), 6.94 (1H, d, J=8Hz), 7.03 (1H, s), 7.30  
10 (1H, t, J=8Hz), 7.45-7.56 (1H, m), 7.90 (1H x 1/3,  
d, J=8Hz), 8.12 (1H x 2/3, d, J=8Hz), 8.26 (1H x  
1/3, d, J=8Hz), 8.54 (1H x 2/3, d, J=8Hz), 8.77 (1H  
x 1/3, s), 9.64 (1H x 2/3, s)

15 Example 18

To a solution of 4-(2,3-diaminobenzoyl)amino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide (640 mg) in dichloromethane (6 ml) were added pyridine (99 mg) and  
20 N-phthaloylglycyl chloride (280 mg) under nitrogen in ice water bath and the mixture was stirred at the same temperature for 2 hours. To the reaction mixture was added methanol (1 ml) at ambient temperature and stirred for additional 30 minutes. The reaction mixture was concentrated  
25 in vacuo and the residue was dissolved in pyridine (6 ml). The solution was stirred at 100°C for 48 hours and the solvent was evaporated in vacuo. The residue was diluted with chloroform and saturated aqueous sodium bicarbonate solution. The organic layer was separated and washed with  
30 water and brine. The organic solution was dried over magnesium sulfate and the solvent was evaporated in vacuo. The residue was chromatographed on silica gel eluting with a mixture of chloroform and methanol (50:1-25:1-10:1) to give  
35 3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]-4-(2-phthalimidomethyl-1H-

benzimidazol-4-yl)carbonylaminobenzamide (410 mg) as a powder.

5 NMR (CDCl<sub>3</sub>, δ) : 1.43-1.61 (2H, m), 1.61-1.76 (2H, m),  
1.76-1.89 (2H, m), 2.27 (3H, s), 2.30 (3H, s),  
2.32-2.43 (6H, m), 3.33 (3H, s), 3.45-3.53 (2H, m),  
3.59-3.67 (2H, m), 3.81-4.02 (5H, m), 5.18 (2H, s),  
6.54-6.65 (2H, m), 6.77-7.03 (3H, m), 7.27-7.38  
10 (1H, m), 7.50 (1H, d, J=8Hz), 7.64-7.77 (2H, m),  
7.77-7.90 (2H, m), 8.10 (1H, d, J=8Hz), 8.46 (1H,  
d, J=8Hz)

#### Example 19

The following compounds were obtained according to a similar manner to that of Example 18.

15

1) 3-Methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]-4-[2-(2-phthalimidoethyl)-1H-benzimidazol-4-yl]carbonylaminobenzamide

20 NMR (CDCl<sub>3</sub>, δ) : 1.46-1.66 (2H, m), 1.66-1.79 (2H, m),  
1.79-1.92 (2H, m), 2.20-2.32 (6H, m), 2.32-2.43  
(6H, m), 3.33 (3H, s), 3.40 (2H, t, J=7Hz), 3.44-  
3.55 (2H, m), 3.55-3.68 (2H, m), 3.81-4.03 (5H, m),  
4.23 (2H, t, J=7Hz), 6.55-6.69 (2H, m), 6.81-7.05  
(3H, m), 7.34 (1H, t, J=8Hz), 7.53-7.62 (2H, m),  
25 7.65-7.76 (2H, m), 7.76-7.91 (1H, m), 8.12 (1H, d,  
J=8Hz), 8.42 (1H, d, J=8Hz)

2) 3-Methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]-4-[2-(2-pyridylmethyl)-1H-benzimidazol-4-yl]carbonylaminobenzamide

30 NMR (CDCl<sub>3</sub>, δ) : 1.46-1.62 (2H, m), 1.62-1.91 (4H, m),  
2.22-2.30 (6H, m), 2.30-2.42 (6H, m), 3.34 (3H, s),  
3.44-3.52 (2H, m), 3.58-3.67 (2H, m), 3.77-4.02  
(5H, m), 4.47 (2H x 1/6, s), 4.52 (2H x 5/6, s),  
35 6.54-6.65 (2H, m), 6.87 (1H, d, J=8Hz), 6.96 (1H,

d, J=8Hz), 7.01-7.09 (1H, m), 7.16-7.35 (overlapped in CHCl<sub>3</sub>), 7.40 (1H x 5/6, d, J=8Hz), 7.48 (1H x 1/6, d, J=8Hz), 7.58 (1H x 5/6, d, J=8Hz), 7.63 (1H x 1/6, d, J=8Hz), 7.66-7.76 (1H, m), 7.89 (1H x 1/6, d, J=8Hz), 8.13 (1H x 5/6, d, J=8Hz), 8.30 (1H x 1/6, d, J=8Hz), 8.51 (1H x 5/6, d, J=8Hz), 8.67 (1H x 5/6, d, J=5Hz), 8.73 (1H x 1/5, s-like)

3) 3-Methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]-4-[2-(3-pyridylmethyl)-1H-benzimidazol-4-yl]carbonylaminobenzamide

NMR (CDCl<sub>3</sub>, δ) : 1.45-1.58 (2H, m), 1.64-1.75 (2H, m), 1.75-1.89 (2H, m), 2.25 (3H, s), 2.29 (3H, s), 2.32-2.43 (6H, m), 3.34 (3H, s), 3.43-3.53 (2H, m), 3.57-3.66 (2H, m), 3.74 (3H x 2/3, s), 3.79 (3H x 1/3, s), 3.81-3.91 (1H, m), 3.90-4.00 (1H, m), 4.32 (2H, s), 6.54-6.64 (2H, m), 6.83-6.92 (1H, m), 6.92-7.03 (2H, m), 7.23-7.36 (overlapped in CHCl<sub>3</sub>), 7.50 (1H, d, J=8Hz), 7.66 (1H x 1/3, d, J=8Hz), 7.73 (1H x 2/3, d, J=8Hz), 7.91 (1H x 1/3, d, J=8Hz), 8.15 (1H x 2/3, d, J=8Hz), 8.21 (1H x 1/3, d, J=8Hz), 8.48-8.75 (3H, m)

4) 3-Methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]-4-[2-(4-pyridylmethyl)-1H-benzimidazol-4-yl]carbonylaminobenzamide

NMR (CDCl<sub>3</sub>-CD<sub>3</sub>OD, δ) : 1.47-1.60 (2H, m), 1.60-1.76 (2H, m), 1.76-1.89 (2H, m), 2.26 (3H, s), 2.30 (3H, s), 2.32-2.44 (6H, m), 3.33 (3H, s), 3.46-3.54 (2H, m), 3.58-3.64 (2H, m), 3.68 (3H x 3/4, s), 3.77 (3H x 1/4, s), 3.81-4.01 (2H, m), 4.33 (2H, s), 6.55-6.65 (2H, m), 6.83-6.92 (1H, m), 6.92-7.02 (2H, m), 7.27-7.38 (3H, m), 7.53 (1H, d, J=8Hz), 8.10 (1H, d, J=8Hz), 8.45-8.55 (3H, m)

Example 20

To a mixture of 4-[(indol-4-yl)carbonyl]amino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide (150 mg) and  
5 N,N-dimethylaminopyridine (5.9 mg) in acetonitrile (10 ml) was added diethyl dicarbonate (46.6 mg) at ambient temperature. The solution was stirred at ambient temperature for a few hours and stood overnight. The resulting mixture was diluted with water and the aqueous solution was extracted  
10 with ethyl acetate. Drying, filtering and removal of solvents afforded a crude product. The crude product was purified by column chromatography (eluent; 2% methanol in chloroform) to give 4-[(1-ethoxycarbonylindol-4-yl)carbonyl]-amino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-  
15 1-yl)carbonylpent-1-yloxy]phenyl]benzamide (126 mg) as a colorless syrup.

NMR (CDCl<sub>3</sub>, δ) : 1.49 (3H, t, J=8Hz), 1.50-1.59 (2H, m), 1.66-1.76 (2H, m), 1.79-1.88 (2H, m), 2.28 (3H, s), 2.29 (3H, s), 2.32-2.41 (6H, m), 3.33 (3H, s),  
20 3.47-3.51 (2H, m), 3.60-3.66 (2H, m), 3.79 (3H, s), 3.88-4.00 (2H, m), 4.50 (2H, q, J=8Hz), 6.59 (1H, d, J=8Hz), 6.64 (1H, s), 6.87 (1H, d, J=8Hz), 6.96 (1H, d, J=8Hz), 7.05 (1H, s), 7.18 (1H, d, J=4Hz), 7.40 (1H, t, J=8Hz), 7.62 (1H, d, J=8Hz), 7.75 (1H, d, J=4Hz),  
25 8.32 (1H, d, J=8Hz), 8.40 (1H, d, J=8Hz), 8.57 (1H, s)

Example 21

30 A solution of 4-[[1-(4-toluenesulfonyl)indol-4-yl]-carbonyl]amino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide (255 mg) in a mixture of 2N potassium hydroxide aqueous solution (2.5 ml) and methanol (6.0 ml) was stirred at  
35 ambient temperature for 3 hours and stood overnight. The

resulting mixture was diluted with water and the solution was extracted with ethyl acetate. Drying, filtering and removal of solvents afforded a crude product. The crude product was chromatographed on silica gel (eluent; 3-8% methanol in chloroform) to give 4-[(indol-4-yl)carbonyl]amino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)-carbonylpent-1-yloxy]phenyl]benzamide (154 mg) as a white amorphous powder.

NMR (CDCl<sub>3</sub>, δ) : 1.48-1.59 (2H, m), 1.66-1.88 (4H, m), 2.29 (3H, s), 2.30 (3H, s), 2.32-2.47 (6H, m), 3.33 (3H, s), 3.48-3.53 (2H, m), 3.62-3.69 (2H, m), 3.77 (3H, s), 3.84-4.00 (2H, m), 6.60 (1H, d, J=8Hz), 6.63 (1H, s), 6.88 (1H, d, J=8Hz), 6.96 (1H, d, J=8Hz), 6.99-7.05 (2H, m), 7.21-7.28 (1H, m), 7.35 (1H, d, J=3Hz), 7.55 (1H, d, J=8Hz), 7.61 (1H, d, J=8Hz), 8.38 (1H, d, J=8Hz), 8.73 (1H, s), 8.82-8.87 (1H, br s)

#### Example 22

To a solution of 4-[(1-pivaloyloxymethylindol-7-yl)carbonyl]amino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide (100 mg) in methanol (4.0 ml) was added 28% sodium methylate in methanol solution (100 mg). The solution was stirred at ambient temperature for a few hours and stood overnight. The resulting mixture was diluted with water and the solution was extracted with ethyl acetate. Drying, filtering and removal of solvents afforded 4-[(indol-7-yl)carbonyl]amino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)-carbonylpent-1-yloxy]phenyl]benzamide (70 mg) as a slightly yellow syrup.

NMR (CDCl<sub>3</sub>, δ) : 1.49-1.95 (6H, m), 2.27 (3H, s), 2.28 (3H, s), 2.32-2.41 (6H, m), 3.33 (3H, s), 3.47-3.51 (2H, m), 3.60-3.67 (2H, m), 3.80 (3H, m), 3.83-3.95 (2H, m), 6.56-6.65 (3H, m), 6.87 (1H, d, J=8Hz),

6.98 (1H, d, J=8Hz), 7.03 (1H, s), 7.16 (1H, t, J=8Hz), 7.32 (1H, d, J=4Hz), 7.49 (1H, d, J=8Hz), 7.83 (1H, d, J=8Hz), 8.30 (1H, d, J=8Hz), 8.78 (1H, s)

5

Example 23

The mixture of 4-[(1-tert-butoxycarbonyl-2-ethoxycarbonylindol-4-yl)carbonyl]amino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide (75 mg) in trifluoroacetic acid (2.0 ml) was stirred at ambient temperature for 5 minutes. Trifluoroacetic acid was removed in vacuo and the residue was diluted with aqueous saturated sodium bicarbonate solution. The solution was extracted with ethyl acetate and the organic layer was washed with brine. Drying, filtering and removal of solvents afforded 4-[(2-ethoxycarbonylindol-4-yl)carbonyl]amino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide (50 mg) as a yellow amorphous powder.

20 NMR (CDCl<sub>3</sub>, δ) : 1.42 (3H, t, J=8Hz), 1.49-1.60 (2H, m), 1.68-1.90 (4H, m), 2.28 (3H, s), 2.29 (3H, s), 2.32-2.43 (6H, m), 3.33 (3H, s), 3.47-3.52 (2H, m), 3.60-3.68 (2H, m), 3.80 (3H, s), 3.87-4.00 (2H, m), 4.41 (2H, q, J=8Hz), 6.60 (1H, d, J=8Hz), 6.63 (1H, s), 6.87 (1H, d, J=8Hz), 6.96 (1H, d, J=8Hz), 7.06 (1H, s), 7.39 (1H, t, J=8Hz), 7.58-7.66 (2H, m), 7.75 (1H, s), 8.35 (1H, d, J=8Hz), 8.68 (1H, s), 9.22-9.28 (1H, br s)

30 Example 24

A mixture of 4-(3-benzyl-2-methoxymethyl-3H-benzimidazol-4-yl)carbonylamino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide (200 mg) and 5% formic acid in methanol solution (10 ml) was refluxed for 24 hours. The reaction

35

mixture was concentrated in vacuo and the residue was dissolved in chloroform. The solution was washed with saturated aqueous sodium bicarbonate solution and the organic layer was dried over magnesium sulfate. The solvent was evaporated in vacuo and the residue was purified by preparative thin-layer chromatography (chloroform-methanol = 10:1) to give 3-methoxy-4-(2-methoxymethyl-1H-benzimidazol-4-yl)carbonylamino-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide (48 mg) as a powder.

NMR (CDCl<sub>3</sub>,  $\delta$ ) : 1.24-1.60 (2H, m), 1.60-1.93 (6H, m), 3.33 (3H, s), 3.42-3.60 (5H, m), 3.60-3.76 (2H, m), 3.76-4.04 (5H, m), 4.77 (2H x 1/3, s), 4.83 (2H x 2/3, s), 6.51-6.67 (2H, m), 6.67-7.10 (3H, m), 7.23-7.56 (2H, m), 7.62 (1H x 2/3, d, J=8Hz), 7.85-7.96 (1H x 1/3, m), 7.17 (1H x 2/3, d, J=8Hz), 8.24-8.33 (1H x 1/3, m), 8.49 (1H x 2/3, d, J=8Hz), 8.72-8.80 (1H x 1/3, m), 9.72 (1H x 2/3, s), 10.91 (1H x 1/3, s)

#### Example 25

A solution of 3-methoxy-4-[1-(4-methoxybenzyl)-2-(N-methylcarbamoyl)-1H-benzimidazol-4-yl]carbonylamino-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide (130 mg) in trifluoroacetic acid (3 ml) was stirred at 60°C for 8 hours. The reaction mixture was concentrated in vacuo and the residue was diluted with a mixture of chloroform and saturated aqueous sodium bicarbonate solution. The organic layer was separated and washed with water and brine. The solution was dried over magnesium sulfate and the solvent was evaporated in vacuo. The residue was purified by preparative thin-layer chromatography (chloroform-methanol = 10:1) to give 3-methoxy-N-methyl-4-[2-(N-methylcarbamoyl)-1H-benzimidazol-4-yl]carbonylamino-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)-

carbonylpent-1-yloxy]phenyl]benzamide (45 mg) as a powder.

NMR (CDCl<sub>3</sub>, δ) : 1.46-1.76 (4H, m), 1.76-1.90 (2H, m),  
2.27 (3H, s), 2.29 (3H, s), 2.31-2.42 (6H, m), 3.19  
(3H, d, J=5Hz), 3.34 (3H, s), 3.44-3.51 (2H, m),  
3.58-3.65 (2H, m), 3.80-4.01 (5H, m), 6.59 (1H, d,  
J=8Hz), 6.64 (1H, s), 6.86 (1H, d, J=8Hz), 6.96  
(1H, d, J=8Hz), 7.09 (1H, s), 7.50 (1H, t, J=8Hz),  
7.66 (1H, br peak), 7.73 (1H, d, J=8Hz), 8.25 (1H,  
d, J=8Hz), 8.51 (1H, d, J=8Hz)

#### Example 26

To a solution of 3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]-4-(2-phthalimidomethyl-1H-benzimidazol-4-yl)carbonylamino benzamide (383 mg) in ethanol (5 ml) was added hydrazine monohydrate (19 mg) at ambient temperature and the solution was stirred at 60°C for 1 hour. The reaction mixture was stirred in an ice water bath for 2 hours and the precipitate was filtered off. The filtrate was evaporated in vacuo and the residue was purified by preparative thin-layer chromatography (chloroform-methanol-ammonia solution (28%) = 160:32:1) to give 4-(2-aminomethyl-1H-benzimidazol-4-yl)carbonylamino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide (200 mg) as a powder.

NMR (CDCl<sub>3</sub>, δ) : 1.45-1.62 (2H, m), 1.64-1.75 (2H, m),  
1.75-1.90 (2H, m), 2.25 (3H, s), 2.29 (3H, s),  
2.31-2.48 (6H, m), 3.33 (3H, s), 3.44-3.54 (2H, m),  
3.58-3.67 (2H, m), 3.71 (3H, s), 3.79-3.90 (1H, m),  
3.90-4.02 (1H, m), 4.20 (2H, br peak), 6.53-6.65  
(2H, m), 6.83-7.04 (3H, m), 7.22-7.32 (1H, m), 7.54  
(1H, br peak), 7.98 (1H, br peak), 8.47 (1H, br  
peak)

#### Example 27



The following compound was obtained according to a similar manner to that of Example 26.

4-[2-(2-Aminoethyl)-1H-benzimidazol-4-yl]carbonylamino-  
3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide

NMR (CDCl<sub>3</sub>, δ) : 1.43-1.58 (2H, m), 1.58-1.90 (4H, m),  
2.25 (3H, s), 2.28 (3H, s), 2.30-2.41 (6H, m),  
3.08-3.16 (2H, m), 3.23-3.34 (5H, m), 3.43-3.51  
(2H, m), 3.56-3.65 (2H, m), 3.76-3.88 (4H, m),  
3.88-4.00 (1H, m), 6.54-6.63 (1H, m), 6.86 (1H, d,  
J=8Hz), 6.91-7.01 (2H, m), 7.28 (1H, t, J=8Hz),  
7.60 (1H, d, J=8Hz), 8.00 (1H, br peak), 9.46 (1H,  
d, J=8Hz)

#### Example 28

A solution of 3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]-4-(3-nitro-2-trifluoroacetylaminobenzoyl)aminobenzamide (10.5 g) in hydrazine monohydrate (100 ml) was stirred at 60°C for 2 hours and the mixture was diluted with a mixture of water and ethyl acetate. The organic layer was separated and washed with saturated aqueous sodium bicarbonate solution and brine. The organic layer was dried over magnesium sulfate and the solution was concentrated in vacuo. The residue was purified by silica gel column chromatography (3% methanol in chloroform) to give 4-(2-amino-3-nitrobenzoyl)amino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)-carbonylpent-1-yloxy]phenyl]benzamide as a yellow powder (5.90 g).

NMR (CDCl<sub>3</sub>, δ) : 1.47-1.58 (2H, m), 1.60-1.88 (4H, m),  
2.28 (3H, s), 2.30 (3H, s), 2.33-2.41 (6H, m), 3.34  
(3H, s), 3.48-3.50 (2H, m), 3.62-3.66 (2H, m), 3.78  
(3H, s), 3.83-3.97 (2H, m), 6.58-6.72 (3H, m), 6.87  
(1H, d, J=6Hz), 6.97 (1H, d, J=6Hz), 7.02 (1H, s),

7.21 (1H, d, J=6Hz), 8.12-8.15 (3H, m), 8.29-8.33 (2H, m)

#### Example 29

5 The solution of 4-[(2-ethoxycarbonylindol-4-yl)-carbonyl]amino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide (100 mg) in a mixture of 1N aqueous sodium hydroxide solution (0.43 ml) and ethanol (4.0 ml) was stirred at ambient  
10 temperature for 5.5 hours. The resulting solution was neutralized with 1N hydrochloric acid and methanol was removed in vacuo. The residue was diluted with water and the aqueous layer was extracted with chloroform. Drying, filtering and removal of solvents afforded 4-[(2-carboxyindol-4-yl)carbonyl]amino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide (70 mg) as a yellow amorphous.

15 NMR (DMSO-d<sub>6</sub>, δ) : 1.38-1.58 (4H, m), 1.69-1.79 (2H, m), 2.19 (3H, s), 2.23 (3H, s), 2.26-2.37 (6H, m),  
20 3.19 (3H, s), 3.38-3.47 (3H, m), 3.70 (3H, s), 3.80-4.00 (3H, m), 6.66 (1H, d, J=8Hz), 6.83 (1H, s), 6.90-6.97 (2H, m), 7.03 (1H, d, J=8Hz), 7.33 (1H, t, J=8Hz), 7.47 (1H, s), 7.58-7.67 (2H, m), 7.90 (1H, d, J=8Hz), 9.20 (1H, s)

#### Example 30

25 To a mixture of 4-[(2-carboxyindol-4-yl)carbonyl]amino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide (60 mg), N,N-dimethylamine hydrochloride (7.7 mg) and 1-hydroxybenzotriazole (14.5 mg) in N,N-dimethylformamide (3.0 ml) was added a solution of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (20.6 mg) in N,N-dimethylformamide (1.0 ml) and the mixture  
30 was stirred at ambient temperature for 4 hours. The resulting mixture was diluted with ethyl acetate and the

organic layer was washed successively with saturated aqueous sodium bicarbonate solution and brine. Drying, filtering and removal of solvents afforded 4-[(2-dimethylaminocarbonyl-indol-4-yl)carbonyl]amino-3-methoxy-N-methyl-N-[4-methyl-2-  
5 [5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]-benzamide (60 mg) as a yellow amorphous powder.

NMR (CDCl<sub>3</sub>, δ) : 1.50-1.61 (2H, m), 1.68-1.90 (4H, m),  
2.29 (6H, s), 2.32-2.42 (6H, m), 3.18-3.27 (3H, br  
s), 3.34 (3H, s), 3.43-3.52 (5H, m), 3.60-3.68 (2H,  
10 m), 3.78 (3H, s), 3.87-4.00 (2H, m), 6.60 (1H, d,  
J=8Hz), 6.64 (1H, s), 6.87 (1H, d, J=8Hz), 6.96  
(1H, d, J=8Hz), 7.07 (1H, s), 7.34 (1H, t, J=8Hz),  
7.45 (1H, s), 7.52 (1H, d, J=8Hz), 7.61 (1H, d,  
J=8Hz), 8.33 (1H, d, J=8Hz), 8.62 (1H, s), 9.73-  
15 9.78 (1H, br s)

### Example 31

A solution of 3-methoxy-4-(2-methoxy-1H-benzimidazol-4-yl)carbonylamino-N-methyl-N-[4-methyl-2-[5-(4-  
20 methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide (139 mg) in 10% hydrogen chloride in methanol (2 ml) was stirred at ambient temperature for 2 hours and 4N hydrogen chloride in 1,4-dioxane (2 ml) was added to the mixture. After being allowed to stand at ambient temperature  
25 overnight, the reaction mixture was concentrated in vacuo and the residue was diluted with a mixture of chloroform and saturated aqueous sodium bicarbonate solution. The organic layer was separated and washed with water and brine. The solution was dried over magnesium sulfate and evaporated in  
30 vacuo. The residue was purified by preparative thin-layer chromatography (chloroform-methanol = 10:1) to give 4-(2-hydroxy-1H-benzimidazol-4-yl)carbonylamino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide (53 mg) as a powder.

35 NMR (CDCl<sub>3</sub>, δ) : 1.44-1.65 (2H, m), 1.65-1.76 (2H, m),

1.76-1.92 (2H, m), 2.28 (3H, s), 2.30 (3H, s),  
2.31-2.43 (6H, m), 3.33 (3H, s), 3.44-3.53 (2H, m),  
3.58-3.69 (2H, m), 3.82 (3H, s), 3.85-4.01 (2H, m),  
6.55-6.68 (2H, m), 6.87 (1H, d, J=8Hz), 6.96 (1H,  
5 d, J=8Hz), 7.05 (1H, s), 7.08-7.21 (2H, m), 8.25  
(1H, d, J=8Hz), 8.50 (1H, s), 8.66 (1H, s), 9.43  
(1H, br s)

### Example 32

10 To a solution of 4-(2-tert-butyldiphenylsiloxymethyl-1H-  
benzimidazol-4-yl)carbonylamino-3-methoxy-N-methyl-N-[4-  
methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-  
yloxy]phenyl]benzamide (296 mg) in dry tetrahydrofuran (10  
ml) was added tetrabutylammonium fluoride (173 mg) in ice  
15 water bath under nitrogen and the mixture was stirred at the  
same temperature for 1 hour. The reaction mixture was  
concentrated in vacuo and the residue was dissolved in  
chloroform. The solution was washed with water and brine and  
dried over magnesium sulfate. The solvent was evaporated in  
20 vacuo. The residue was purified by preparative thin-layer  
chromatography (chloroform-methanol = 10:1) to give 4-(2-  
hydroxymethyl-1H-benzimidazol-4-yl)carbonylamino-3-methoxy-N-  
methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-  
1-yloxy]phenyl]benzamide (200 mg) as a powder.

25 NMR (CDCl<sub>3</sub>, δ) : 1.37-1.58 (2H, m), 1.58-1.90 (4H, m),  
2.23 (3H, s), 2.28 (3H, s), 2.30-2.44 (6H, m), 3.32  
(3H, s), 3.40-3.71 (7H, m), 3.71-3.88 (1H, m),  
3.88-4.01 (1H, m), 4.85 (2H, s), 6.58 (2H, s-like),  
6.67-6.79 (1H, m), 6.79-6.97 (2H, m), 7.14-7.30  
30 (1H, m), 7.49 (1H, br peak), 7.98 (1H, br peak),  
8.36 (1H, d, J=8Hz)

### Example 33

A mixture of 4-(2-amino-1H-benzimidazol-4-yl)-  
35 carbonylamino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-

methylnpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide (45 mg) and acetic anhydride (0.5 ml) was stirred at ambient temperature for 1 hour and then allowed to stand at the same temperature overnight. The reaction mixture was concentrated in vacuo and the residue was dissolved in chloroform. The solution was washed successively with saturated aqueous sodium bicarbonate solution, water and brine and the solution was dried over magnesium sulfate. The solvent was evaporated in vacuo and the residue was purified by preparative thin-layer chromatography (chloroform-methanol = 10:1) to give 4-(2-acetamido-1H-benzimidazol-4-yl)carbonylamino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylnpiperazin-1-yl)-carbonylpent-1-yloxy]phenyl]benzamide (26 mg) to give a powder.

NMR (CDCl<sub>3</sub>, δ) : 1.36-1.52 (2H, br peak), 1.58-1.82 (4H, m), 2.26 (3H, s), 2.28-2.42 (15H, m), 3.32 (3H, s), 3.43-3.51 (2H, m), 3.51-3.66 (5H, m), 3.75 (1H, br peak), 3.91 (1H, br peak), 6.55-6.65 (2H, m), 6.84-6.95 (2H, m), 6.99 (1H, s), 7.20-7.31 (1H, m), 7.54 (1H, br peak), 8.07 (1H, br peak), 8.34 (1H, d, J=8Hz)

#### Example 34

To a solution of 4-(2-amino-1H-benzimidazol-4-yl)carbonylamino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylnpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide (90 mg) in pyridine (1 ml) was added methanesulfonyl chloride (18 mg) in ice water bath under nitrogen and the mixture was stirred at the same temperature for 3 hours. The reaction mixture was concentrated in vacuo and the residue was dissolved in chloroform. The organic layer was washed successively with saturated aqueous sodium bicarbonate solution, water and brine and the solution was dried over magnesium sulfate. The solvent was evaporated in vacuo and the residue was purified by preparative thin-layer

chromatography (chloroform-methanol = 10:1) to give 4-(2-methanesulfonylamino-1H-benzimidazol-4-yl)carbonylamino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide (15 mg) as a powder.

5 NMR (CDCl<sub>3</sub>, δ) : 1.42-1.58 (2H, m), 1.62-1.95 (4H, m),  
2.26 (3H, s), 2.29-2.45 (9H, m), 3.24 (3H, s), 3.34  
(3H, s), 3.44-3.52 (2H, m), 3.59-3.67 (2H, m),  
3.76-3.89 (4H, m), 3.89-4.00 (1H, m), 6.98 (1H, br  
s), 6.54-6.65 (2H, m), 6.88 (1H, d, J=8Hz), 6.94  
10 (1H, d, J=8Hz), 7.04 (1H, s), 7.23 (1H, t, J=8Hz),  
7.74 (1H, d, J=8Hz), 8.11 (1H, d, J=8Hz), 8.40 (1H,  
d, J=8Hz)

#### Example 35

15 The following compound was obtained according to a  
similar manner to that of Example 34.

4-(2-Benzenesulfonylamino-1H-benzimidazol-4-yl)carbonyl-  
amino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-  
20 1-yl)carbonylpent-1-yloxy]phenyl]benzamide

NMR (CDCl<sub>3</sub>, δ) : 1.43-1.73 (4H, m), 1.73-1.84 (2H, m),  
2.25 (3H, s), 2.30 (3H, s), 2.31-2.42 (6H, m), 3.33  
(3H, s), 3.44-3.51 (2H, m), 3.59-3.66 (2H, m),  
3.75-3.87 (4H, m), 3.87-4.00 (1H, m), 6.04 (2H, s),  
25 6.54-6.63 (2H, m), 6.86 (1H, d, J=8Hz), 6.93 (1H,  
d, J=8Hz), 7.20 (1H, t, J=8Hz), 7.48-7.56 (2H, m),  
7.65 (1H, t, J=8Hz), 7.85 (1H, d, J=8Hz), 7.97 (2H,  
d, J=8Hz), 8.08 (1H, d, J=8Hz), 8.37 (1H, d,  
J=8Hz), 11.39 (1H, s)

30

#### Example 36

To a solution of 4-[(indol-4-yl)carbonyl]amino-3-  
methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-  
yl)carbonylpent-1-yloxy]phenyl]benzamide (93 mg) in  
35 dichloromethane (6.0 ml) was added N,N-dimethylmethylen-

ammonium chloride (41.7 mg) at 0°C and the mixture was stirred at ambient temperature for 1 hour. The resulting mixture was diluted with water and the aqueous solution was extracted with dichloromethane. Drying, filtering and  
5 removal of solvents afforded 4-[(3-dimethylaminomethylindol-4-yl)carbonylamino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide (90 mg) as a colorless syrup.

NMR (CDCl<sub>3</sub>, δ) : 1.50-1.95 (6H, m), 2.28 (3H, s), 2.29  
10 (6H, s), 2.30 (3H, s), 2.33-2.42 (6H, m), 3.34 (3H, s), 3.44-3.52 (2H, m), 3.60-3.66 (2H, m), 3.68 (3H, s), 3.84-4.00 (2H, m), 5.30 (2H, s), 6.58 (1H, d, J=8Hz), 6.62 (1H, s), 6.83 (1H, d, J=8Hz), 6.93 (1H, d, J=8Hz), 6.97 (1H, s), 7.10-7.26 (2H, m),  
15 7.35-7.57 (3H, m), 8.23-8.31 (1H, m), 8.36-8.40 (1H, br)

#### Example 37

To a mixture of 4-(2-hydroxymethyl-1H-benzimidazol-4-yl)carbonylamino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide (40 mg), triethylamine (31 mg), dimethyl sulfoxide (0.5 ml) and dichloromethane (0.5 ml) was added portionwise sulfur trioxide pyridine complex (29 mg) in water bath and the  
25 mixture was stirred at the same temperature for 1 day. The reaction mixture was poured into saturated aqueous sodium bicarbonate solution and the solution was extracted with chloroform. The organic layer was washed with water and brine and the solution was dried over magnesium sulfate. The  
30 solvent was evaporated in vacuo and the residue was purified by preparative thin-layer chromatography (chloroform-methanol = 10:1) to give 4-(2-formyl-1H-benzimidazol-4-yl)carbonylamino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide (6  
35 mg) as a powder.

NMR (CDCl<sub>3</sub>, δ) : 1.47-1.64 (2H, m), 1.64-1.90 (4H, m),  
2.25 (3H, s), 2.29 (3H, s), 2.34-2.44 (6H, m),  
3.23-3.38 (3H, m), 3.46-3.54 (2H, m), 3.60-3.68  
(2H, m), 3.73-4.01 (5H, m), 6.54-6.66 (2H, m),  
5 6.83-7.10 (3H, m), 7.47-7.63 (1H, m), 7.63-7.77  
(1H, m), 8.07-8.80 (3H, m), 9.96-10.12 (1H, m),  
11.85 (1H, br s)

#### Example 38

10 To a solution of 4-(2-amino-3-nitrobenzoyl)amino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide (50 mg) in ethanol (2 ml) was added 1N hydrochloric acid (0.16 ml) at ambient temperature and allowed to stand at the same temperature for  
15 30 minutes. After being removed the solvent under reduced pressure, the resulting solid was dissolved in distilled water (5 ml) and the solution was filtered through micro filter. The filtrate was lyophilized to give 4-[(2-amino-3-nitro)benzoyl]amino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide  
20 dihydrochloride (48 mg) as a white powder.

NMR (DMSO-d<sub>6</sub>, δ) : 1.37-1.51 (2H, m), 1.51-1.65 (2H, m), 1.65-1.84 (2H, m), 2.22 (3H, s), 2.33-2.45 (2H, m), 2.77 (3H, s), 2.81-3.46 (9H, m), 3.61 (3H, s),  
25 3.80-3.91 (1H, m), 3.91-4.00 (1H, m), 4.00-4.16 (1H, m), 4.23-4.51 (1H, m), 6.65 (1H, d, J=8Hz), 6.73 (1H, t, J=8Hz), 6.82 (1H, s-like), 6.86-6.96 (2H m), 7.05 (1H, d, J=8Hz), 7.52 (1H, d, J=8Hz), 7.96 (1H, d, J=8Hz), 7.99-8.08 (2H, m), 8.21 (1H, d, J=8Hz),  
30 9.63 (1H, s)

#### Example 39

The following compounds were obtained according to a similar manner to that of Example 38.



1) 4-[(Indol-4-yl)carbonyl]amino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]-phenyl]benzamide hydrochloride

5 NMR (DMSO-d<sub>6</sub>, δ) : 1.42-1.63 (4H, m), 1.71-1.80 (2H, m), 2.25 (3H, s), 2.37-2.42 (2H, m), 2.73 (3H, s), 2.89-3.03 (3H, m), 3.20 (3H, s), 3.31-3.48 (3H, m), 3.70 (3H, s), 3.85-4.10 (3H, m), 4.39-4.49 (1H, m), 6.67 (1H, d, J=9Hz), 6.82 (2H, s), 6.90-6.98 (2H, m), 7.04 (1H, d, J=9Hz), 7.19 (1H, t, J=8Hz), 7.51-7.58 (2H, m), 7.62 (1H, d, J=8Hz), 8.00 (1H, d, J=8Hz), 9.05 (1H, s)

2) 4-[(1-Methylindol-4-yl)carbonyl]amino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide hydrochloride

15 NMR (DMSO-d<sub>6</sub>, δ) : 1.42-1.63 (4H, m), 1.71-1.80 (2H, m), 2.25 (3H, s), 2.40 (2H, t, J=8Hz), 2.73 (3H, s), 2.90-3.05 (3H, m), 3.19 (3H, s), 3.30-3.45 (3H, m), 3.70 (3H, s), 3.87 (3H, s), 3.88-4.00 (3H, m), 4.39-4.47 (1H, m), 6.67 (1H, d, J=8Hz), 6.80 (1H, d, J=3Hz), 6.83 (1H, s), 6.91-6.97 (2H, m), 7.06 (1H, d, J=8Hz), 7.27 (1H, t, J=8Hz), 7.51 (1H, d, J=3Hz), 7.58 (1H, d, J=8Hz), 7.69 (1H, d, J=8Hz), 7.98 (1H, d, J=8Hz), 9.07 (1H, s)

25 3) 4-[(1-Ethoxycarbonylindol-4-yl)carbonyl]amino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide hydrochloride

30 NMR (DMSO-d<sub>6</sub>, δ) : 1.41 (3H, t, J=8Hz), 1.42-1.63 (4H, m), 1.71-1.81 (2H, m), 2.23 (3H, s), 2.39 (2H, t, J=8Hz), 2.74 (3H, s), 2.86-3.04 (3H, m), 3.19 (3H, s), 3.30-3.48 (3H, m), 3.67 (3H, s), 3.83-4.00 (4H, m), 4.48 (2H, q, J=8Hz), 6.66 (1H, d, J=8Hz), 6.82 (1H, s), 6.90-6.96 (2H, m), 7.05 (1H, d, J=8Hz), 7.10 (1H, d, J=4Hz), 7.47 (1H, t, J=8Hz), 7.72-7.81

(2H, m), 7.83 (1H, d, J=4Hz), 8.31 (1H, d, J=8Hz),  
9.33 (1H, s)

4) 4-[(1-Isopropylindol-4-yl)carbonyl]amino-3-methoxy-N-  
5 methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-  
1-yloxy]phenyl]benzamide hydrochloride

NMR (DMSO-d<sub>6</sub>, δ) : 1.41-1.67 (4H, m), 1.48 (6H, d,  
J=7Hz), 1.71-1.81 (2H, m), 2.23 (3H, s), 2.39 (2H,  
t, J=8Hz), 2.73 (3H, s), 2.90-3.05 (3H, m), 3.19  
10 (3H, s), 3.29-3.45 (3H, m), 3.69 (3H, s), 3.84-4.00  
(4H, m), 4.80-4.90 (1H, m), 6.67 (1H, d, J=8Hz),  
6.80-6.87 (2H, m), 6.90-6.97 (2H, m), 7.05 (1H, d,  
J=8Hz), 7.25 (1H, t, J=8Hz), 7.55 (1H, d, J=8Hz),  
7.69 (1H, d, J=3Hz), 7.77 (1H, d, J=8Hz), 7.98 (1H,  
15 d, J=8Hz), 9.06 (1H, s)

5) 4-[(3-Dimethylaminomethylindol-4-yl)carbonyl]amino-3-  
methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-  
yl)carbonylpent-1-yloxy]phenyl]benzamide dihydrochloride

20 NMR (DMSO-d<sub>6</sub>, δ) : 1.42-1.64 (4H, m), 1.71-1.82 (2H,  
m), 2.24 (3H, s), 2.40 (2H, t, J=8Hz), 2.70 (3H,  
s), 2.72 (6H, s), 2.82-3.08 (4H, m), 3.20 (3H, s),  
3.38-3.54 (3H, m), 3.68 (3H, s), 3.84-4.11 (3H, m),  
5.63-5.72 (2H, br s), 6.66 (1H, d, J=8Hz), 6.83  
25 (1H, s), 6.90-6.98 (2H, m), 7.04 (1H, d, J=8Hz),  
7.27 (1H, t, J=8Hz), 7.38-7.52 (2H, m), 7.60-7.78  
(2H, m), 8.02-8.18 (2H, m)

6) 4-[(Indol-7-yl)carbonyl]amino-3-methoxy-N-methyl-N-[4-  
30 methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-  
yloxy]phenyl]benzamide hydrochloride

NMR (DMSO-d<sub>6</sub>, δ) : 1.41-1.62 (4H, m), 1.70-1.81 (2H,  
m), 2.23 (3H, s), 2.39 (2H, t, J=8Hz), 2.74 (3H,  
s), 2.88-3.02 (3H, m), 3.20 (3H, s), 3.30-3.42 (3H,  
35 m), 3.66 (3H, s), 3.85-4.03 (3H, m), 4.38-4.47 (1H,

m), 6.51 (1H, d, J=3Hz), 6.67 (1H, d, J=8Hz), 6.83 (1H, s), 6.89-6.98 (2H, m), 7.06 (1H, d, J=8Hz), 7.10 (1H, d, J=8Hz), 7.37 (1H, d, J=3Hz), 7.71-7.80 (3H, m), 9.35 (1H, s)

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7) 4-[(1-Methylindol-7-yl)carbonyl]amino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide hydrochloride

NMR (DMSO-d<sub>6</sub>, δ) : 1.40-1.80 (6H, m), 2.22 (3H, s),  
10 2.39 (2H, t, J=8Hz), 2.72 (3H, s), 2.91-3.02 (3H, m), 3.18 (3H, s), 3.31-3.48 (3H, m), 3.63 (3H, s), 3.73 (3H, s), 3.87-4.12 (3H, m), 4.39-4.48 (1H, m), 6.51 (1H, d, J=3Hz), 6.67 (1H, d, J=8Hz), 6.83 (1H, s), 6.89-7.09 (3H, m), 7.20-7.29 (2H, m), 7.37 (1H, d, J=3Hz), 7.68 (1H, d, J=8Hz), 7.80 (1H, d, J=8Hz), 9.53 (1H, s)

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8) 4-[(2-Ethoxycarbonylindol-4-yl)carbonyl]amino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide hydrochloride

NMR (DMSO-d<sub>6</sub>, δ) : 1.37 (3H, t, J=8Hz), 1.43-1.63 (4H, m), 1.72-1.80 (2H, m), 2.24 (3H, s), 2.40 (2H, t, J=8Hz), 2.73 (3H, s), 2.88-3.03 (3H, m), 3.20 (3H, s), 3.28-3.45 (4H, m), 3.70 (3H, s), 3.87-4.00 (3H, m), 4.37 (2H, q, J=8Hz), 6.67 (1H, d, J=8Hz), 6.83 (1H, s), 6.90-6.97 (2H, m), 7.07 (1H, d, J=8Hz), 7.38 (1H, t, J=8Hz), 7.56 (1H, s), 7.61-7.69 (2H, m), 7.86 (1H, d, J=8Hz), 9.27 (1H, s)

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9) 4-[(2-Dimethylaminocarbonylindol-4-yl)carbonyl]amino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide hydrochloride

NMR (DMSO-d<sub>6</sub>, δ) : 1.42-1.63 (4H, m), 1.72-1.81 (2H, m), 2.25 (3H, s), 2.40 (2H, t, J=8Hz), 2.74 (3H, s), 2.97-3.13 (3H, m), 3.19 (3H, s), 3.30-3.49

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(10H, m), 3.68 (3H, s), 3.88-4.08 (3H, m), 6.67 (1H, d, J=8Hz), 6.83 (1H, s), 6.90-6.97 (2H, m), 7.05 (1H, d, J=8Hz), 7.21 (1H, s), 7.30 (1H, t, J=8Hz), 7.59 (1H, d, J=8Hz), 7.65 (1H, d, J=8Hz), 7.90 (1H, d, J=8Hz), 9.20 (1H, s)

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10) 4-[1H-Imidazo[4,5-b]pyridin-7-yl]carbonylamino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide trihydrochloride

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NMR (DMSO-d<sub>6</sub>, δ) : 1.39-1.67 (4H, m), 1.69-1.83 (2H, m), 2.22 (3H, s), 2.39 (2H, t, J=7Hz), 2.72 and 2.74 (Total 3H, s), 2.80-3.11 (3H, m), 3.20 (3H, s), 3.31-3.57 (3H, m), 3.76 (3H, s), 3.80-4.77 (4H, m), 6.66 (1H, d, J=8Hz), 6.82 (1H, s), 6.89-7.01 (2H, m), 7.05 (1H, d, J=8Hz), 7.82 (1H, d, J=7Hz), 8.28 (1H, d, J=8Hz), 8.57 (1H, d, J=7Hz), 8.79 (1H, s)

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11) 4-[2-Chloro-1H-benzimidazol-4-yl]carbonylamino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide dihydrochloride

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NMR (DMSO-d<sub>6</sub>, δ) : 1.37-1.66 (4H, m), 1.67-1.83 (2H, m), 2.21 (3H, s), 2.39 (2H, t, J=7Hz), 2.73 (3H, s), 2.80-3.09 (3H, m), 3.19 (3H, s), 3.29-3.60 (3H, m), 3.71-4.17 (6H, m), 4.43 (1H, m), 6.64 (1H, d, J=8Hz), 6.81 (1H, s), 6.87-6.99 (2H, m), 7.03 (1H, d, J=8Hz), 7.41 (1H, dd, J=8, 8Hz), 7.72 (1H, d, J=8Hz), 7.96 (1H, d, J=8Hz), 8.33 (1H, d, J=8Hz)

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12) 4-(2,3-Diaminobenzoyl)amino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide trihydrochloride

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NMR (DMSO-d<sub>6</sub>, δ) : 1.38-1.52 (2H, m), 1.52-1.66 (2H, m), 1.66-1.83 (2H, m), 2.23 (3H, s), 2.40 (2H, t, J=7Hz), 2.75 (3H, s), 2.81-3.11 (3H, m), 3.18 (3H,

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s), 3.28-3.50 (3H, m), 3.63 (3H, s), 3.82-3.92 (1H, m), 3.92-4.03 (1H, m), 4.45 (1H, br peak), 6.60-6.77 (2H, m), 6.83 (1H, s-like), 6.87-6.98 (2H, m), 7.05 (1H, d, J=8Hz), 7.23 (1H, d, J=8Hz), 7.50 (1H, d, J=8Hz), 7.60 (1H, d, J=8Hz), 9.31 (1H, s)

13) 4-[2-Guanidinobenzimidazol-4-yl]carbonylamino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)-carbonylpent-1-yloxy]phenyl]benzamide dihydrochloride

10 NMR (DMSO-d<sub>6</sub>, δ) : 1.31-1.84 (6H, m), 2.22 (3H, s), 2.40 (2H, t, J=7Hz), 2.74 (3H, s), 2.80-3.11 (3H, m), 3.18 (3H, s), 3.26-3.63 (3H, m), 3.74 (3H, s), 3.80-4.20 (3H, m), 4.33-4.53 (1H, m), 6.64 (1H, d, J=8Hz), 6.82 (1H, s), 6.92 (1H, d, J=8Hz), 6.99 (1H, s), 7.04 (1H, d, J=8Hz), 7.33 (1H, dd, J=8, 8Hz), 7.69 (1H, d, J=8Hz), 7.90 (1H, d, J=8Hz), 8.28-8.41 (1H, m), 8.49-8.80 (3H, m)

14) 4-(1H-Benzimidazol-4-yl)carbonylamino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide dihydrochloride

20 NMR (DMSO-d<sub>6</sub>, δ) : 1.40-1.51 (2H, m), 1.51-1.64 (2H, m), 1.69-1.81 (2H, m), 2.22 (3H, s), 2.39 (2H, t, J=7.5Hz), 2.49 (3H, s), 2.75 (3H, d-like), 2.80-3.07 (3H, m), 3.19 (3H, s), 3.31-3.48 (3H, m), 3.73 (3H, s), 3.77-4.03 (2H, m), 4.03-4.14 (1H, m), 4.38-4.50 (1H, m), 6.65 (1H, d, J=8Hz), 6.81 (1H, s-like), 6.87-6.98 (2H, m), 7.04 (1H, d, J=8Hz), 7.43 (1H, t, J=8Hz), 7.83 (1H, d, J=8Hz), 7.98 (1H, d, J=8Hz), 8.24 (1H, br peak), 8.64 (1H, br s), 10.63 (1H, br peak)

15) 4-(2-Hydroxy-1H-benzimidazol-4-yl)carbonylamino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide hydrochloride

NMR (DMSO-d<sub>6</sub>, δ) : 1.39-1.52 (2H, m), 1.52-1.65 (2H, m), 1.69-1.82 (2H, m), 2.22 (3H, s), 2.39 (2H, t, J=7.5Hz), 2.76 (3H, d-like), 2.80-3.08 (3H, m), 3.19 (3H, s), 3.27-3.45 (3H, m), 3.64 (3H, s), 3.81-3.91 (1H, m), 3.91-4.01 (1H, m), 4.01-4.14 (1H, m), 4.38-4.50 (1H, m), 6.65 (1H, d, J=8Hz), 6.83 (1H, s), 6.86-6.96 (2H, m), 6.96-7.12 (3H, m), 7.46 (1H, d, J=8Hz), 7.66 (1H, d, J=8Hz) 9.28 (1H, s)

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16) 3-Methoxy-N-methyl-4-(2-methyl-1H-benzimidazol-4-yl)-carbonylamino-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide dihydrochloride

NMR (DMSO-d<sub>6</sub>, δ) : 1.39-1.51 (2H, m), 1.52-1.65 (2H, m), 1.65-1.82 (2H, m), 2.23 (3H, s), 2.39 (2H, t, J=7.5Hz), 2.68 (3H, s), 2.75 (3H, d-like), 2.79-3.09 (3H, m), 3.18 (3H, s), 3.30-3.44 (3H, m), 3.72 (3H, s), 3.80-3.90 (1H, m), 3.90-4.00 (1H, m), 4.00-4.13 (1H, m), 4.48-4.50 (1H, m), 6.65 (1H, d, J=8Hz), 6.82 (1H, s-like), 6.87-6.98 (2H, m), 7.04 (1H, d, J=8Hz), 7.39 (1H, br peak), 7.77 (1H, br peak), 7.95 (1H, br peak), 10.67 (1H, br s)

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17) 4-(2-Mercapto-1H-benzimidazol-4-yl)carbonylamino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide dihydrochloride

NMR (DMSO-d<sub>6</sub>, δ) : 1.39-1.52 (2H, m), 1.52-1.65 (2H, m), 1.70-1.82 (2H, m), 2.23 (3H, s), 2.40 (2H, t, J=7Hz), 2.76 (3H, s), 3.20 (3H, s), 3.65 (3H, s), 3.80-4.06 (2H, m), 6.65 (1H, d, J=8Hz), 6.83 (1H, s), 7.05 (1H, d, J=8Hz), 7.20 (1H, t, J=8Hz), 7.30 (1H, d, J=8Hz), 7.60 (1H, d, J=8Hz), 7.64-7.71 (2H, m), 9.11 (1H, s), 9.50 (1H, s)

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18) 3-Methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-

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1-yl)carbonylpent-1-yloxy]phenyl]-4-(2-trifluoromethyl-1H-benzimidazol-4-yl)carbonylamino benzamide dihydrochloride

5 NMR (DMSO-d<sub>6</sub>, δ) : 1.39-1.53 (2H, m), 1.53-1.65 (2H, m), 1.65-1.83 (2H, m), 2.22 (3H, s), 2.40 (2H, t, J=7Hz), 2.78 (3H, s), 2.82-3.07 (3H, m), 3.20 (3H, s), 3.28-3.51 (3H, m), 3.75 (3H, s), 3.80-3.91 (1H, m), 3.91-4.03 (1H, m), 4.10 (1H, br peak), 4.43 (1H, br peak), 6.66 (1H, d, J=8Hz), 6.82 (1H, s), 6.90-7.00 (2H, m), 7.04 (1H, d, J=8Hz), 7.61 (1H, t, J=8Hz), 7.94 (1H, d, J=8Hz), 8.11 (1H, d, J=8Hz), 8.41 (1H, d, J=8Hz), 10.33 (1H, br peak), 11.89 (1H, s)

15 19) 4-(2-Amino-1H-benzimidazol-4-yl)carbonylamino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)-carbonylpent-1-yloxy]phenyl]benzamide dihydrochloride

20 NMR (DMSO-d<sub>6</sub>, δ) : 1.37-1.53 (2H, m), 1.53-1.65 (2H, m), 1.70-1.84 (2H, m), 2.23 (3H, s), 2.39 (2H, t, J=7.5Hz), 2.75 (3H, s), 2.80-3.10 (3H, m), 3.20 (3H, s), 3.26-3.55 (3H, m), 3.66 (3H, s), 3.78-3.92 (1H, m), 3.91-4.01 (1H, m), 4.07 (1H, br s), 4.43 (1H, br s), 6.65 (1H, d, J=8Hz), 6.83 (1H, s), 6.87-6.98 (2H, m), 7.04 (1H, d, J=8Hz), 7.29 (1H, br peak), 7.55 (1H, br peak), 7.86 (1H, br peak), 8.20 (1H, br peak), 9.75 (1H, br peak), 10.78 (1H, br peak)

30 20) 4-(2-Acetamido-1H-benzimidazol-4-yl)carbonylamino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)-carbonylpent-1-yloxy]phenyl]benzamide dihydrochloride

35 NMR (CD<sub>3</sub>OD, δ) : 1.50-1.65 (2H, m), 1.65-1.77 (2H, m), 1.77-1.92 (2H, m), 2.28 (3H, s), 2.35 (3H, s), 2.51 (2H, t-like), 2.93 (3H, s), 2.96-3.59 (6H, m), 3.75 (3H, s), 3.81-3.95 (1H, m), 3.95-4.07 (1H, m), 4.15-4.31 (1H, m), 4.57-4.71 (1H, m), 6.70 (1H, d,

J=8Hz), 6.80 (1H, s-like), 6.94 (1H, s-like), 7.00-7.12 (2H, m), 7.47-7.58 (2H, m), 7.81 (1H, d, J=8Hz), 7.99 (1H, d, J=8Hz), 8.06 (1H, d, J=8Hz)

- 5 21) 4-(2-Methanesulfonylamino-1H-benzimidazol-4-yl)-  
carbonylamino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-  
methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide  
dihydrochloride

10 NMR (CD<sub>3</sub>OD,  $\delta$ ) : 1.50-1.64 (2H, m), 1.64-1.77 (2H, m),  
1.77-1.90 (2H, m), 2.28 (3H, s), 2.50 (2H, t,  
J=7Hz), 2.92 (3H, s), 2.95-3.20 (3H, m), 3.39-3.60  
(5H, m), 3.76 (3H, s), 3.83-3.94 (1H, m), 3.94-4.07  
(1H, m), 4.17-4.32 (1H, m), 4.60-4.72 (1H, m), 6.70  
(1H, d, J=8Hz), 6.79 (1H, s), 6.92 (1H, s), 6.99-  
15 7.10 (2H, m), 7.30 (1H, t, J=8Hz), 7.88 (1H, d,  
J=8Hz), 7.95 (1H, d, J=8Hz), 8.18 (1H, d, J=8Hz)

- 22) 4-(2-Benzenesulfonylamino-1H-benzimidazol-4-yl)-  
carbonylamino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-  
20 methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide  
dihydrochloride

25 NMR (DMSO-d<sub>6</sub>,  $\delta$ ) : 1.35-1.50 (2H, m), 1.50-1.65 (2H,  
m), 1.65-1.80 (2H, m), 2.21 (3H, s), 2.38 (2H, t,  
J=7.5Hz), 2.75 (3H, d, J=5Hz), 2.80-3.10 (3H, m),  
3.17 (3H, s), 3.25-3.48 (3H, m), 3.73 (3H, s),  
3.78-3.90 (1H, m), 3.90-4.00 (1H, m), 4.07 (1H, br  
d, J=15Hz), 4.44 (1H, br d, J=15Hz), 6.54 (1H, d,  
J=8Hz), 6.78-6.98 (3H, m), 7.04 (1H, d, J=8Hz),  
7.19 (1H, t, J=8Hz), 7.53-7.73 (3H, m), 7.73-7.94  
30 (3H, m), 8.12 (2H, d, J=8Hz), 8.25 (1H, d, J=8Hz)

- 23) 4-(1H-Benzotriazol-4-yl)carbonylamino-3-methoxy-N-  
methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-  
1-yloxy]phenyl]benzamide hydrochloride

35 NMR (DMSO-d<sub>6</sub>,  $\delta$ ) : 1.39-1.52 (2H, m), 1.52-1.66 (2H,



5 m), 1.70-1.83 (2H, m), 2.22 (3H, s), 2.39 (2H, t, J=8Hz), 2.77 (3H, s), 2.83-3.10 (3H, m), 3.20 (3H, s), 3.25-3.53 (3H, m), 3.77 (3H, s), 3.82-3.93 (1H, m), 3.93-4.03 (1H, m), 4.08 (1H, br peak), 4.45 (1H, br peak), 6.66 (1H, d, J=8Hz), 6.82 (1H, s), 6.92-7.01 (2H, m), 7.06 (1H, d, J=8Hz), 7.72 (1H, br peak), 8.06-8.19 (2H, m), 8.36 (1H, br peak), 10.37 (1H, br peak), 11.56 (1H, br peak)

10 24) 4-(2-Ethyl-1H-benzimidazol-4-yl)carbonylamino-3-methoxy-N-methyl-N-[4-methyl-2-{5-(4-methylpiperazin-1-yl)-carbonylpent-1-yloxy}phenyl]benzamide dihydrochloride

15 NMR (DMSO-d<sub>6</sub>, δ) : 1.37-1.52 (5H, m), 1.52-1.65 (2H, m), 1.68-1.83 (2H, m), 2.23 (3H, s), 2.40 (2H, t, J=7.5Hz), 2.75 (3H, d, J=5Hz), 2.82-3.08 (5H, m), 3.18 (3H, s), 3.30-3.60 (3H, m), 3.73 (3H, s), 3.81-3.91 (1H, m), 3.91-4.02 (1H, m), 4.10 (1H, br d, J=15Hz), 4.45 (1H, br d, J=15Hz), 6.65 (1H, d, J=8Hz), 6.81 (1H, s), 6.89-6.99 (2H, m), 7.04 (1H, d, J=8Hz), 7.30-7.41 (1H, m), 7.73 (1H, d, J=8Hz), 7.92 (1H, d, J=8Hz), 8.33 (1H, br peak), 10.49 (1H, br s)

25 25) 3-Methoxy-N-methyl-N-[4-methyl-2-{5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy}phenyl]-4-(2-n-propyl-1H-benzimidazol-4-yl)carbonylaminobenzamide dihydrochloride

30 NMR (DMSO-d<sub>6</sub>, δ) : 0.99 (3H, t, J=7.5Hz), 1.38-1.52 (2H, m), 1.52-1.67 (2H, m), 1.67-1.83 (2H, m), 1.83-1.98 (2H, m), 2.23 (3H, s), 2.40 (2H, t, J=7.5Hz), 2.76 (3H, d, J=4Hz), 2.82-3.08 (5H, m), 3.20 (3H, s), 3.33-3.66 (3H, m), 3.73 (3H, s), 3.81-3.93 (1H, m), 3.93-4.03 (1H, m), 4.10 (1H, br d, J=15Hz), 4.44 (1H, br d, J=15Hz), 6.65 (1H, d, J=8Hz), 6.82 (1H, s), 6.89-6.98 (2H, m), 7.04 (1H, d, J=8Hz), 7.31-7.43 (1H, m), 7.75 (1H, br d,

J=8Hz), 7.94 (1H, br d, J=8Hz), 8.26 (1H, br peak)

26) 4-(2-Isopropyl-1H-benzimidazol-4-yl)carbonylamino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide dihydrochloride

NMR (DMSO-d<sub>6</sub>, δ) : 1.37-1.51 (8H, m), 1.51-1.65 (2H, m), 1.65-1.84 (2H, m), 2.23 (3H, s), 2.40 (2H, t, J=7.5Hz), 2.76 (3H, d, J=4Hz), 2.83-3.09 (3H, m), 3.19 (3H, s), 3.23-3.43 (4H, m), 3.73 (3H, s), 3.81-3.92 (1H, m), 3.92-4.03 (1H, m), 4.09 (1H, br d, J=15Hz), 4.45 (1H, br d, J=15Hz), 6.65 (1H, d, J=8Hz), 6.81 (1H, s), 6.90-6.97 (2H, m), 7.04 (1H, d, J=8Hz), 7.34 (1H, t, J=8Hz), 7.71 (1H, d, J=8Hz), 7.90 (1H, d, J=8Hz), 8.38 (1H, br peak)

27) 4-(2-Aminomethyl-1H-benzimidazol-4-yl)carbonylamino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide trihydrochloride

NMR (DMSO-d<sub>6</sub>, δ) : 1.39-1.53 (2H, m), 1.53-1.66 (2H, m), 1.66-1.83 (2H, m), 2.23 (3H, s), 2.40 (2H, t, J=7Hz), 2.76 (3H, d-like), 2.82-3.10 (3H, m), 3.19 (3H, s), 3.75 (3H, s), 3.88 (1H, br peak), 3.98 (1H, br peak), 4.04-4.15 (1H, m), 4.38-4.50 (3H, m), 6.65 (1H, d, J=8Hz), 6.83 (1H, s), 6.95 (2H, br peak), 7.05 (1H, d, J=8Hz), 7.43 (1H, t, J=8Hz), 7.85 (1H, d, J=8Hz), 7.98 (1H, d, J=8Hz), 8.33 (1H, br peak), 8.75 (2H, br peak)

28) 4-[2-(2-Aminoethyl)-1H-benzimidazol-4-yl]carbonylamino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide trihydrochloride

NMR (DMSO-d<sub>6</sub>, δ) : 1.38-1.51 (2H, m), 1.51-1.65 (1H, m), 1.65-1.83 (2H, m), 2.22 (3H, s), 2.40 (2H, t, J=7.5Hz), 2.74 (3H, d, J=4Hz), 2.80-3.11 (3H, m), 3.30-3.50 (5H, m), 3.92-4.02 (1H, m), 4.10 (1H, br

5 d, J=15Hz), 4.44 (1H, br d, J=15Hz), 6.66 (1H, d, J=8Hz), 6.83 (1H, s), 6.90-7.00 (2H, m), 7.05 (1H, d, J=8Hz), 7.36 (1H, t, J=8Hz), 7.75 (1H, d, J=8Hz), 7.93 (1H, d, J=8Hz), 8.16-8.31 (3H, m), 8.31-8.42 (1H, m)

29) 3-Methoxy-N-methyl-4-(3-methyl-3H-benzimidazol-4-yl)carbonylamino-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)-carbonylpent-1-yloxy]phenyl]benzamide dihydrochloride

10 NMR (CD<sub>3</sub>OD,  $\delta$ ) : 1.49-1.66 (2H, m), 1.66-1.79 (2H, m), 1.79-1.94 (2H, m), 2.27 (3H, s), 2.51 (2H, t, J=7.5Hz), 2.91 (3H, s), 2.95-3.35 (3H, m), 3.35-3.61 (3H, m), 3.71 (3H, s), 3.81-4.07 (2H, m), 4.10 (3H, s), 4.23 (1H, br peak), 4.65 (1H, br peak),  
15 6.69 (1H, d, J=8Hz), 6.79 (1H, s-like), 6.97 (1H, s), 7.01-7.09 (2H, m), 7.70 (1H, t, J=8Hz), 7.82 (1H, d, J=8Hz), 7.95-8.08 (2H, m), 9.34 (1H, s)

30) 3-Methoxy-4-(2-methoxymethyl-1H-benzimidazol-4-yl)-carbonylamino-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide dihydrochloride

20 NMR (DMSO-d<sub>6</sub>,  $\delta$ ) : 1.38-1.52 (2H, m), 1.52-1.65 (2H, m), 1.65-1.82 (2H, m), 2.22 (3H, s), 2.39 (2H, t, J=7Hz), 2.75 (3H, d-like), 2.80-3.09 (3H, m), 3.20 (3H, s), 3.32-3.53 (6H, m), 3.77 (3H, s), 3.81-3.91 (1H, m), 3.91-4.00 (1H, m), 4.04-4.14 (1H, m),  
25 4.40-4.50 (1H, m), 4.80 (2H, s), 6.65 (1H, d, J=8Hz), 6.80 (1H, s-like), 6.89-6.98 (2H, m), 7.04 (1H, d, J=8Hz), 7.37 (1H, t, J=8Hz), 7.74 (1H, d, J=8Hz),  
30 7.94 (1H, d, J=8Hz), 8.37 (1H, d, J=8Hz), 10.55 (1H, br s)

31) 4-(1,2-Dimethyl-1H-benzimidazol-4-yl)carbonylamino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide dihydrochloride

35

NMR (DMSO-d<sub>6</sub>, δ) : 1.38-1.53 (2H, m), 1.53-1.65 (2H, m), 1.65-1.82 (2H, m), 2.23 (3H, s), 2.40 (2H, t, J=7Hz), 2.70 (3H, s), 2.75 (3H, d-like), 2.80-3.08 (3H, m), 3.19 (3H, s), 3.31-3.50 (3H, m), 3.85 (3H, s), 3.92-4.01 (1H, m), 4.08 (1H, br d, J=12Hz), 4.44 (1H, br d, J=12Hz), 6.66 (1H, d, J=8Hz), 6.82 (1H, s), 6.90-7.00 (2H, m), 7.05 (1H, d, J=8Hz), 7.37-7.50 (1H, m), 7.83-7.92 (1H, m), 7.96 (1H, d, J=8Hz), 8.23 (1H, br peak), 10.78 (1H, br peak)

32) 4-(1-Ethyl-2-methyl-1H-benzimidazol-4-yl)carbonylamino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide dihydrochloride

NMR (DMSO-d<sub>6</sub>, δ) : 1.34 (3H, t, J=7Hz), 1.40-1.53 (2H, m), 1.53-1.66 (2H, m), 1.66-1.83 (2H, m), 2.23 (3H, s), 2.40 (2H, t, J=7Hz), 2.72 (3H, s), 2.75 (3H, d-like), 2.81-3.09 (2H, m), 3.20 (3H, s), 3.30-3.52 (4H, m), 3.75 (3H, s), 4.09 (1H, br d, J=12Hz), 4.35 (2H, q, J=7Hz), 4.44 (1H, br d, J=12Hz), 6.65 (1H, d, J=8Hz), 6.82 (1H, s), 6.90-6.99 (2H, m), 7.04 (1H, d, J=8Hz), 7.42 (1H, t, J=8Hz), 7.90 (1H, d, J=8Hz), 7.96 (1H, d, J=8Hz), 8.25 (1H, br peak)

33) 3-Methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]-4-(2-methyl-1-propyl-1H-benzimidazol-4-yl)carbonylaminobenzamide dihydrochloride

NMR (DMSO-d<sub>6</sub>, δ) : 0.90 (3H, t, J=7Hz), 1.40-1.52 (2H, m), 1.52-1.65 (2H, m), 1.68-1.86 (4H, m), 2.23 (3H, s), 2.39 (2H, t, J=7Hz), 2.70 (3H, s), 2.75 (3H, d, J=5Hz), 2.80-3.07 (3H, m), 3.18 (3H, m), 3.33-3.44 (3H, m), 3.76 (3H, s), 3.86 (1H, br peak), 3.95 (1H, br peak), 4.09 (1H, br d, J=12Hz), 4.27 (1H, t, J=8Hz), 4.44 (1H, br d, J=12Hz), 6.65 (1H, d, J=8Hz), 6.81 (1H, s), 6.88-6.98 (2H, m), 7.05 (1H, d, J=8Hz), 7.39 (1H, t, J=8Hz), 7.87 (1H, d,

J=8Hz), 7.94 (1H, d, J=8Hz), 8.30 (1H, br peak)

34) 3-Methoxy-N-methyl-4-[2-(N-methylcarbamoyl)-1H-benzimidazol-4-yl]carbonylamino-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide dihydrochloride

NMR (DMSO-d<sub>6</sub>, δ) : 1.40-1.53 (2H, m), 1.53-1.65 (2H, m), 1.70-1.83 (2H, m), 2.21 (3H, s), 2.40 (2H, t, J=7Hz), 2.75 (3H, d, J=5Hz), 2.80-3.10 (6H, m), 3.20 (3H, s), 3.33-3.50 (3H, m), 3.76 (3H, s), 3.90 (1H, br peak), 3.97 (1H, br peak), 4.09 (1H, br d, J=12Hz), 4.44 (1H, br d, J=12Hz), 6.65 (1H, d, J=8Hz), 6.83 (1H, s), 6.91-6.99 (2H, m), 7.05 (1H, d, J=8Hz), 7.50 (1H, t, J=8Hz), 7.79 (1H, d, J=8Hz), 8.02 (1H, d, J=8Hz), 8.31 (1H, d, J=8Hz), 8.41 (1H, q-like)

35) 4-(2-Hydroxymethyl-1H-benzimidazol-4-yl)carbonylamino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide dihydrochloride

NMR (DMSO-d<sub>6</sub>, δ) : 1.38-1.52 (2H, m), 1.52-1.67 (2H, m), 1.67-1.83 (2H, m), 2.23 (3H, s), 2.40 (2H, t, J=7.5Hz), 2.78 (3H, d, J=4Hz), 2.82-3.10 (3H, m), 3.20 (3H, s), 3.75 (3H, s), 3.80-3.91 (1H, m), 3.91-4.01 (1H, m), 4.01-4.17 (1H, m), 4.36-4.52 (1H, m), 4.86 (2H, s), 6.64 (1H, d, J=8Hz), 6.81 (1H, s), 6.85-6.98 (2H, m), 7.35 (1H, t, J=8Hz), 7.72 (1H, d, J=8Hz), 7.90 (1H, d, J=8Hz), 8.24-8.37 (1H, m), 10.40 (1H, br peak)

36) 4-(Benzoxazol-4-yl)carbonylamino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide hydrochloride

NMR (DMSO-d<sub>6</sub>, δ) : 1.39-1.51 (2H, m), 1.51-1.65 (2H, m), 1.65-1.82 (2H, m), 2.24 (3H, s), 2.40 (2H, t,

J=7.5Hz), 2.77 (3H, s), 2.81-3.10 (3H, m), 3.20 (3H, s), 3.30-3.45 (3H, m), 3.77 (3H, s), 3.81-3.91 (1H, m), 3.91-4.04 (1H, m), 4.14-4.24 (1H, m), 4.40-4.52 (1H, m), 6.65 (1H, d, J=8Hz), 6.81 (1H, s-like), 6.91-6.99 (2H, m), 7.07 (1H, d, J=8Hz), 7.65 (1H, t, J=8Hz), 8.06-8.14 (2H, m), 8.32 (1H, d, J=8Hz), 9.14 (1H, s)

37) 3-Methoxy-N-methyl-4-(2-methylimidazo[1,2-a]pyridin-4-yl)carbonylamino-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)-carbonylpent-1-yloxy]phenyl]benzamide dihydrochloride

NMR (DMSO-d<sub>6</sub>, δ) : 1.37-1.53 (2H, m), 1.53-1.65 (2H, m), 1.68-1.84 (2H, m), 2.23 (3H, s), 2.40 (2H, t, J=7Hz), 2.46 (3H, s), 2.75 (3H, d-like), 2.80-3.08 (3H, m), 3.20 (3H, s), 3.31-3.53 (3H, m), 3.92-4.01 (1H, m), 4.09 (1H, br d, J=12Hz), 4.45 (1H, br d, J=12Hz), 6.66 (1H, d, J=8Hz), 6.83 (1H, s-like), 6.90-7.00 (2H, m), 7.06 (1H, d, J=8Hz), 7.24 (1H, br peak), 7.99 (1H, br s), 8.07-8.25 (2H, m), 8.76-8.89 (1H, m), 10.94 (1H, br peak)

38) 3-Methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]-4-[2-(2-pyridylmethyl)-1H-benzimidazol-4-yl]carbonylaminobenzamide trihydrochloride

NMR (DMSO-d<sub>6</sub>, δ) : 1.39-1.51 (2H, m), 1.51-1.64 (2H, m), 1.67-1.82 (2H, m), 2.23 (3H, s), 2.40 (2H, t, J=7.5Hz), 2.75 (3H, d, J=5Hz), 2.80-3.07 (3H, m), 3.20 (3H, s), 3.33-3.44 (3H, m), 3.64 (3H, s), 3.66-4.00 (overlapped in H<sub>2</sub>O), 4.02-4.14 (1H, m), 4.39-4.50 (1H, m), 4.67 (2H, s), 6.65 (1H, s, J=8Hz), 6.81 (1H, s), 6.85-6.96 (2H, m), 7.03 (1H, d, J=8Hz), 7.38 (1H, t, J=8Hz), 7.48-7.57 (1H, m), 7.67 (1H, d, J=8Hz), 7.76 (1H, d, J=8Hz), 7.93 (1H, d, J=8Hz), 7.98-8.09 (1H, m), 8.20-8.29 (1H, m), 8.61-8.67 (1H, m)

39) 3-Methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]-4-[2-(3-pyridylmethyl)-1H-benzimidazol-4-yl]carbonylaminobenzamide trihydrochloride

5 NMR (DMSO-d<sub>6</sub>, δ) : 1.39-1.51 (2H, m), 1.51-1.65 (2H, m), 1.65-1.83 (2H, m), 2.23 (3H, s), 2.39 (2H, t, J=7.5Hz), 2.74 (3H, s), 2.80-3.10 (3H, m), 3.20 (3H, s), 3.29-3.52 (3H, m), 3.66 (3H, s), 3.80-3.92 (1H, m), 3.92-4.02 (1H, m), 4.10 (1H, br peak), 4.43 (1H, br peak), 4.61 (2H, s), 6.67 (1H, d, J=8Hz), 6.83 (1H, s), 6.89-6.99 (2H, m), 7.04 (1H, d, J=8Hz), 7.37 (1H, t, J=8Hz), 7.75 (1H, d, J=8Hz), 7.86-7.99 (2H, m), 8.24-8.35 (1H, m), 8.44 (1H, d, J=8Hz), 8.76-8.86 (1H, m), 8.99 (1H, s-like)

10

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40) 3-Methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]-4-[2-(4-pyridylmethyl)-1H-benzimidazol-4-yl]carbonylaminobenzamide trihydrochloride

20 NMR (DMSO-d<sub>6</sub>, δ) : 1.38-1.51 (2H, m), 1.51-1.66 (2H, m), 1.66-1.83 (2H, m), 2.22 (3H, s), 2.39 (2H, t, J=7.5Hz), 2.74 (3H, s), 2.80-3.09 (3H, m), 3.19 (3H, s), 3.30-3.44 (3H, m), 3.63 (3H, s), 3.65-4.00 (overlapped in H<sub>2</sub>O), 4.08 (1H, br peak), 4.44 (1H, br peak), 4.72 (2H, s), 6.65 (1H, d, J=8Hz), 6.82 (1H, s), 6.87-6.95 (2H, m), 7.03 (1H, d, J=8Hz), 7.39 (1H, t, J=8Hz), 7.78 (1H, d, J=8Hz), 7.94 (1H, d, J=8Hz), 8.05 (2H, d, J=5Hz), 8.25-8.35 (1H, m), 8.88 (2H, d, J=5Hz)

25

30 41) 3-Methoxy-4-(2-methoxycarbonylamino-1H-benzimidazol-4-yl)carbonylamino-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide dihydrochloride

35 NMR (DMSO-d<sub>6</sub>, δ) : 1.40-1.52 (2H, m), 1.52-1.66 (2H, m), 1.66-1.81 (2H, m), 2.23 (3H, s), 2.38 (2H, t,

5 J=7.5Hz), 2.75 (3H, d, J=5Hz), 2.81-3.08 (3H, m),  
3.19 (3H, s), 3.32-3.47 (3H, m), 3.74 (3H, s),  
3.79-3.91 (4H, m), 3.91-4.02 (4H, m), 4.07 (1H, br  
d, J=15Hz), 4.44 (1H, br d, J=15Hz), 6.67 (1H, d,  
J=8Hz), 6.82 (1H, s), 6.88 (1H, s), 6.94 (1H, d,  
J=8Hz), 7.05 (1H, d, J=8Hz), 7.23 (1H, t, J=8Hz),  
7.69 (1H, d, J=8Hz), 7.83 (1H, d, J=8Hz), 8.25 (1H,  
d, J=8Hz)

10 Preparation 33

The following compound was obtained by using 2-amino-4-nitro-1H-benzimidazole as a starting compound according to a similar manner to that of Preparation 1.

15 2-[(Methylsulfonyl)amino]-4-nitro-1H-benzimidazole  
NMR (DMSO-d<sub>6</sub>,  $\delta$ ) : 3.61 (3H, s), 7.16 (1H, t, J=8Hz),  
7.75 (2H, br peak), 7.83 (1H, d, J=8Hz), 7.95 (1H,  
d, J=8Hz)

20 Preparation 34

The following compounds were obtained according to a similar manner to that of Preparation 5.

1) N-(2-Chloroethyl)-2-nitrobenzamide  
25 NMR (CDCl<sub>3</sub>,  $\delta$ ) : 3.72-3.89 (4H, m), 6.27 (1H, br), 7.56  
(1H, m), 7.60 (1H, dd, J=8, 8Hz), 7.70 (1H, dd,  
J=8, 8Hz), 8.10 (1H, d, J=8Hz)

2) N-(3-Chloropropyl)-2-nitrobenzamide  
30 NMR (CDCl<sub>3</sub>,  $\delta$ ) : 2.09-2.20 (2H, m), 3.56-3.73 (4H, m),  
6.15 (1H, br s), 7.50 (1H, d, J=8Hz), 7.59 (1H, dd,  
J=8, 8Hz), 7.67 (1H, dd, J=8, 8Hz), 8.05 (1H, d,  
J=8Hz)

35 3) N-[1-(Hydroxymethyl)cyclopentyl]-2-nitrobenzamide



NMR (CDCl<sub>3</sub>,  $\delta$ ) : 1.61-2.00 (8H, m), 3.62 (1H, t, J=7Hz), 3.80 (2H, d, J=7Hz), 6.00 (1H, s), 7.52 (1H, m), 7.59 (1H, m), 7.68 (1H, t, J=8, 8Hz), 8.07 (1H, d, J=8Hz)

5

### Preparation 35

The following compounds were obtained according to a similar manner to that of Preparation 8.

- 10      1) Benzyl 1-tert-butoxycarbonyl-3-tert-butyldiphenyl-silyloxymethylindole-4-carboxylate
- NMR (CDCl<sub>3</sub>,  $\delta$ ) : 1.09 (9H, s), 1.67 (9H, s), 5.03 (2H, s), 5.19 (2H, s), 7.27-7.43 (12H, m), 7.66-7.78 (6H, m), 8.43 (1H, d, J=8Hz)

15

- 2) 2-tert-Butyldiphenylsilyloxymethyl-4-nitro-1H-benzimidazole

NMR (CDCl<sub>3</sub>,  $\delta$ ) : 1.15 (9H, s), 5.08 (2H, s), 7.30-7.51 (7H, m), 7.70 (4H, d-like), 8.00 (1H, d, J=8Hz), 8.15 (1H, d, J=8Hz)

20

### Preparation 36

To a solution of benzyl 2-hydroxymethylindole-4-carboxylate (456 mg) and imidazole (364 mg) in N,N-dimethylformamide (10 ml) was added tert-butyldiphenylsilyl chloride (802 mg) and the solution was stirred at ambient temperature for 2 hours. The resulting mixture was diluted with ethyl acetate (30 ml) and washed successively with water and brine. The organic layer was dried over magnesium sulfate and concentrated in vacuo. The residue was purified by silica gel column chromatography (eluent; n-hexane:ethyl acetate = 15:1) to give benzyl 2-tert-butyldiphenylsilyloxymethylindole-4-carboxylate (810 mg).

NMR (CDCl<sub>3</sub>,  $\delta$ ) : 1.09 (9H, s), 4.93 (2H, s), 5.42 (2H, s), 6.89 (1H, s), 7.19 (1H, t, J=8Hz), 7.30-7.54

35

(12H, m), 7.68 (4H, d, J=8Hz), 7.92 (1H, d, J=8Hz),  
8.32-8.37 (1H, br)

### Preparation 37

5       The following compound was obtained by using methyl 2-formyl-1-methoxymethoxyindole-4-carboxylate as a starting compound according to a similar manner to that of Preparation 10.

10       Methyl 2-hydroxymethylindole-4-carboxylate  
NMR (DMSO-d<sub>6</sub>, δ) : 3.88 (3H, s), 4.67 (2H, d, J=6Hz),  
5.37 (1H, t, J=6Hz), 6.80 (1H, s), 7.13 (1H, t,  
J=8Hz), 7.60 (1H, d, J=8Hz), 7.69 (1H, d, J=8Hz)

### 15       Preparation 38

The following compounds were obtained according to a similar manner to that of Preparation 12.

- 1) 1-tert-Butoxycarbonyl-2-ethoxycarbonylindoline-4-carboxylic acid  
20       NMR (DMSO-d<sub>6</sub>, δ) : 1.22 (3H, t, J=8Hz), 1.45 (9H, s),  
3.37 (1H, dd, J=8, 16Hz), 3.78 (1H, dd, J=10, 16Hz), 4.17 (2H, q, J=8Hz), 4.90 (1H, dd, J=8, 10Hz), 7.32 (1H, t, J=8Hz), 7.51 (1H, d, J=8Hz),  
25       7.94-8.03 (1H, m)
- 2) 1-tert-Butoxycarbonyl-3-tert-butyldiphenylsilyloxy-methylindole-4-carboxylic acid  
NMR (CDCl<sub>3</sub>, δ) : 1.08 (9H, s), 1.68 (9H, s), 5.10 (2H,  
30       s), 7.28-7.41 (7H, m), 7.65-7.70 (4H, m), 7.77 (1H, s), 7.88 (1H, d, J=9Hz), 8.52 (1H, d, J=9Hz)
- 3) 1-tert-Butoxycarbonyl-2-phthalimidomethylindole-4-carboxylic acid  
35       NMR (CDCl<sub>3</sub>, δ) : 1.69 (9H, s), 5.15 (2H, s), 6.86 (1H,

s), 7.37 (1H, t, J=8Hz), 7.80 (1H, d, J=8Hz), 7.89-8.03 (4H, m), 8.28 (1H, d, J=8Hz)

4) 1-tert-Butoxycarbonyl-2-methylindole-4-carboxylic acid

5 NMR (CDCl<sub>3</sub>, δ) : 1.70 (9H, s), 2.67 (3H, s), 7.13 (1H, s), 7.30 (1H, t, J=9Hz), 8.03 (1H, d, J=9Hz), 8.40 (1H, d, J=9Hz)

#### Preparation 39

10 To a solution of benzyl 1-tert-butoxycarbonyl-2-tert-butyl-  
diphenylsilyloxymethylindole-4-carboxylate (762 mg) in  
5.0% formic acid-methanol (20.0 ml) was added 10% palladium  
on carbon (100 mg) and the mixture was stirred under nitrogen  
15 atmosphere at ambient temperature for 2 hours. The resulting  
solution was filtered through a bed of celite and the  
filtrate was concentrated in vacuo. The residue was diluted  
with chloroform (10 ml) and the solution was washed  
successively with water and brine. The organic layer was  
20 dried over magnesium sulfate and concentrated in vacuo to  
give 1-tert-butoxycarbonyl-2-tert-butyl-  
diphenylsilyloxy-  
methylindole-4-carboxylic acid (597 mg).

NMR (CDCl<sub>3</sub>, δ) : 1.13 (9H, s), 1.49 (9H, s), 5.05 (2H, s), 7.29-7.43 (7H, m), 7.57 (1H, s), 7.71 (4H, d, J=8Hz), 8.08 (1H, d, J=8Hz), 8.44 (1H, d, J=8Hz)

25

#### Preparation 40

To a solution of benzyl 1-tert-butoxycarbonylindole-6-  
carboxylate (1.27 g) in 5.0% formic acid-methanol (20.0 ml)  
was added 10% palladium on carbon (1.27 g) and the mixture  
30 was stirred under nitrogen atmosphere at ambient temperature  
for 4 hours and stand overnight. The resulting solution was  
filtered through a bed of celite and the filtrate was  
concentrated in vacuo. The residue was diluted with  
chloroform and the solution was washed successively with  
35 water and brine. The organic layer was dried over magnesium

sulfate and concentrated in vacuo. The residue was triturated with ether:n-hexane (1:5) to give 1-tert-butoxycarbonylindoline-6-carboxylic acid (761 mg).

5 NMR (DMSO- $d_6$ ,  $\delta$ ) : 1.50 (9H, s), 3.11 (2H, t, J=11Hz),  
3.96 (2H, t, J=11Hz), 7.28 (1H, d, J=8Hz), 7.54  
(1H, d, J=8Hz), 8.20-8.30 (1H, br)

#### Preparation 41

10 To a solution of benzyl 1-tert-butoxycarbonylindole-6-carboxylate (450 mg) in 5.0% formic acid-methanol (10.0 ml) was added 10% palladium on carbon (153 mg) and the mixture was stirred under nitrogen atmosphere at ambient temperature for 4 hours. The resulting solution was filtered through a bed of celite and the filtrate was concentrated in vacuo.

15 The residue was diluted with chloroform and the solution was washed successively with water and brine. The organic layer was dried over magnesium sulfate and concentrated in vacuo. The residue was triturated with ether:n-hexane (1:5) to give 1-tert-butoxycarbonylindole-6-carboxylic acid (302 mg).

20 NMR (DMSO- $d_6$ ,  $\delta$ ) : 1.67 (9H, s), 6.80 (1H, d, J=3Hz),  
7.69 (1H, d, J=8Hz), 7.83 (1H, d, J=8Hz), 7.86 (1H, d, J=3Hz), 8.75 (1H, s)

#### Preparation 42

25 The following compound was obtained by using 3-methoxy-4-methoxycarbonyl-N-[4-methyl-2-(4-phthalimidobut-1-yloxy)]-phenylbenzamide as a starting compound according to a similar manner to that of Preparation 15.

30 3-Methoxy-4-methoxycarbonyl-N-methyl-N-[4-methyl-2-(4-phthalimidobut-1-yloxy)]phenylbenzamide

NMR (CDCl<sub>3</sub>,  $\delta$ ) : 1.77-1.91 (4H, m), 2.23 (3H, s), 3.31  
(3H, s), 3.69 (3H, s), 3.77 (2H, t, J=7.5Hz), 3.81  
(3H, s), 3.82-3.99 (2H, m), 6.40-6.50 (2H, m), 6.82  
35 (1H, d, J=8Hz), 6.88 (1H, d, J=8Hz), 6.90 (1H, s),

7.55 (1H, d, J=8Hz), 7.65-7.73 (2H, m), 7.81-7.88 (2H, m)

#### Preparation 43

5 The following compound was obtained according to a similar manner to that of Preparation 42.

3-Methoxy-4-nitro-N-methyl-N-[4-methyl-2-(5-phthalimidopent-1-yloxy)]phenylbenzamide

10 NMR (CDCl<sub>3</sub>, δ) : 1.46-1.58 (2H, m), 1.70-1.91 (4H, m),  
2.27 (3H, s), 3.30 (3H, s), 3.74 (2H, t, J=7.5Hz),  
3.79 (3H, s), 3.85-3.95 (2H, m), 6.57-6.63 (2H, m),  
6.82 (1H, d, J=8Hz), 6.94 (1H, d, J=8Hz), 7.06 (1H, s),  
7.61 (1H, d, J=8Hz), 7.68-7.75 (2H, m), 7.80-  
15 7.85 (2H, m)

#### Preparation 44

The following compounds were obtained according to a similar manner to that of Preparation 17.

20

1) 2-Benzyloxymethyl-1-tert-butoxycarbonylindoline-4-carboxylic acid

NMR (CDCl<sub>3</sub>, δ) : 1.50 (9H, s), 3.45-3.59 (3H, m), 3.67 (1H, dd, J=4, 10Hz), 4.52 (2H, s), 4.57-4.67 (1H, br),  
25 7.21-7.38 (7H, m), 7.70 (1H, d, J=8Hz)

2) 3-Formylindole-4-carboxylic acid

NMR (DMSO-d<sub>6</sub>, δ) : 7.31 (1H, t, J=8Hz), 7.73 (2H, d, J=8Hz), 8.27 (1H, d, J=3Hz), 10.45 (1H, s)

30

3) 2-Hydroxymethylindole-4-carboxylic acid

NMR (CDCl<sub>3</sub>, δ) : 4.65 (2H, s), 5.27-5.40 (1H, br), 6.82 (1H, s), 7.10 (1H, t, J=8Hz), 7.57 (1H, d, J=8Hz), 7.67 (1H, d, J=8Hz)

35

- 4) 4-Carboxy-3-methoxy-N-methyl-N-(4-methyl-2-nitrophenyl)benzamide

NMR (CDCl<sub>3</sub>, δ) : 2.24 (3H, s), 3.43 (3H, s), 3.97 (3H, s), 6.80 (1H, d, J=8Hz), 7.09 (1H, s), 7.20 (1H, d, J=8Hz), 7.34 (1H, d, J=8Hz), 7.60 (1H, s), 7.89 (1H, d, J=8Hz)

- 5) 4-Carboxy-3-methoxy-N-methyl-N-[2-(4-tert-butoxycarbonylaminobut-1-yl)oxy-4-methyl]phenylbenzamide

NMR (CDCl<sub>3</sub>, δ) : 1.45 (9H, s), 1.60-1.72 (2H, m), 1.76-1.87 (2H, m), 2.26 (3H, s), 3.19 (2H, t, J=7.5Hz), 3.32 (3H, s), 3.81-3.97 (2H, m), 3.89 (3H, s), 6.57-6.62 (2H, m), 7.85 (1H, d, J=8Hz), 7.98 (1H, d, J=8Hz), 7.07 (1H, s), 7.90 (1H, s)

- 6) 4-Carboxy-N-[2-[4,4-dimethyl(2,5-oxazolinyl)]phenyl]-N-methyl-3-methoxybenzamide

NMR (CDCl<sub>3</sub>, δ) : 1.36 (3H, s), 1.37 (3H, s), 3.37 (3H, s), 3.81 (3H, s), 4.02-4.18 (2H, m), 7.01-7.18 (3H, m), 7.21-7.39 (2H, m), 7.79 (1H, m), 7.91 (1H, d, J=8Hz)

- 7) 4-Carboxy-3-methoxy-N-methyl-N-[2-(morpholin-4-yl)phenyl]benzamide

NMR (CDCl<sub>3</sub>, δ) : 2.28-2.43 (2H, m), 2.78-2.92 (2H, m), 3.52 (3H, s), 3.59-3.85 (7H, m), 6.86 (1H, d, J=8Hz), 7.04 (1H, s), 7.08-7.18 (2H, m), 7.21 (1H, d, J=8Hz), 7.29 (1H, dd, J=8, 8Hz), 7.92 (1H, d, J=8Hz)

- 8) 4-Carboxy-3-methoxy-N-methyl-N-[2-(1-pyrrolyl)phenyl]benzamide

NMR (CDCl<sub>3</sub>, δ) : 3.51 (3H, s), 3.88 (3H, s), 6.25 (2H, s), 6.32-6.41 (2H, m), 6.53 (1H, d, J=8Hz), 6.60 (1H, s), 7.11 (1H, m), 7.26-7.52 (3H, m), 7.75 (1H,

d, J=8Hz)

- 9) 4-Carboxy-3-methoxy-N-methyl-N-(2-piperidinophenyl)-benzamide

5 NMR (CDCl<sub>3</sub>, δ) : 1.41-1.71 (6H, m), 2.20-2.36 (2H, m),  
2.68-2.83 (2H, m), 3.52 (3H, s), 3.79 (3H, s), 6.83  
(1H, d, J=8Hz), 6.96-7.30 (5H, m), 7.92 (1H, d,  
J=8Hz)

- 10 10) 4-Carboxy-N-methyl-3-methoxy-N-[2-(4-methyl-1-piperazinyl)phenyl]benzamide

NMR (DMSO-d<sub>6</sub>, δ) : 2.22 (3H, s), 2.23-2.50 (6H, m),  
2.70-2.91 (2H, m), 3.36 (3H, s), 3.50 (3H, s), 6.81  
(1H, s), 6.86-7.00 (2H, m), 7.10 (1H, m), 7.19 (1H,  
15 m), 7.32-7.46 (2H, m)

- 11) 4-Carboxy-3-methoxy-N-methyl-N-[2-(2,5-oxazolyl)phenyl]-benzamide

20 NMR (CDCl<sub>3</sub>, δ) : 3.46 (3H, s), 3.78 (3H, s), 6.77-6.85  
(2H m), 7.23-7.46 (4H, m), 7.75-7.91 (3H, m)

- 12) 4-Carboxy-N-methyl-3-methoxy-N-[2-(2,5-oxazolinyl)-phenyl]benzamide

25 NMR (CDCl<sub>3</sub>, δ) : 3.41 (3H, s), 3.82 (3H, s), 4.02-4.17  
(2H, m), 4.32-4.50 (2H, m), 7.00-7.08 (2H, m), 7.15  
(1H, d, J=8Hz), 7.28 (1H, dd, J=8, 8Hz), 7.38 (1H,  
dd, J=8, 8Hz), 7.77 (1H, m), 7.89 (1H, d, J=8Hz)

- 13) 4-Carboxy-N-methyl-3-methoxy-N-[2-(3H,4H,5H-2,6-oxazinyl)phenyl]benzamide

30 NMR (CDCl<sub>3</sub>, δ) : 1.94-2.08 (2H, m), 3.42 (3H, s), 3.58  
(2H, t, J=7Hz), 3.78 (3H, s), 4.29-4.41 (2H, m),  
6.84-7.37 (4H, m), 7.48-7.60 (2H, m), 7.90 (1H, d,  
J=8Hz).

- 14) N-[2-(1-(Aza-3-oxaspiro[4.4]non-1-en-2-yl)phenyl)-4-carboxy-3-methoxy-N-methylbenzamide

NMR (CDCl<sub>3</sub>, δ) : 1.61-1.77 (4H, m), 1.82-2.04 (4H, m),  
3.38 (3H, s), 3.82 (3H, s), 4.16-4.28 (2H, m),  
7.06-7.16 (3H, m), 7.22-7.39 (2H, m), 7.77 (1H, m),  
7.92 (1H, d, J=8Hz)

- 15) 2-Carbamoyl-1-(4-methoxybenzyl)-1H-benzimidazole-4-carboxylic acid

NMR (DMSO-d<sub>6</sub>, δ) : 3.69 (3H, s), 5.89 (3H, s), 6.86  
(2H, d, J=8Hz), 7.23 (2H, d, J=8Hz), 7.30 (1H, t,  
J=8Hz), 7.66 (1H, d, J=8Hz), 7.72 (1H, d, J=8Hz),  
7.89 (1H, br s), 9.30 (1H, br peak)

- 16) 2-(N,N-Dimethylcarbamoyl)-1-(4-methoxybenzyl)-1H-benzimidazole-4-carboxylic acid

NMR (DMSO-d<sub>6</sub>, δ) : 2.91 (3H, s), 3.05 (3H, s), 3.71  
(3H, s), 5.49 (2H, s), 6.89 (2H, d, J=8Hz), 7.22  
(2H, d, J=8Hz), 7.42 (1H, t, J=8Hz), 7.82 (1H, d,  
J=8Hz), 7.92 (1H, d, J=8Hz)

- 17) 2-[1-(Benzyloxycarbonyl)-4-piperidyl]-1H-benzimidazole-4-carboxylic acid

NMR (DMSO-d<sub>6</sub>, δ) : 1.69-1.88 (2H, m), 1.95-2.08 (2H,  
m), 2.99 (2H, br peak), 3.24-3.59 (1H, m), 4.08-  
4.19 (2H, m), 5.10 (2H, s), 7.23-7.47 (6H, m), 7.79  
(1H, d, J=8Hz), 7.85 (1H, d, J=8Hz)

- 18) 2-(N-tert-Butoxycarbonylaminomethyl)-1-methyl-1H-benzimidazole-4-carboxylic acid

NMR (DMSO-d<sub>6</sub>, δ) : 1.36 (9H, s), 4.01 (3H, s), 4.77  
(2H, d, J=5Hz), 7.16-7.31 (2H, m), 8.11 (1H, d,  
J=8Hz), 8.23 (1H, d, J=8Hz)

- 19) 2-(N-tert-Butoxycarbonylaminomethyl)-3-methyl-3H-



benzimidazole-4-carboxylic acid

NMR (DMSO-d<sub>6</sub>, δ) : 1.40 (9H, s), 3.96 (3H, s), 4.65 (2H, d, J=6Hz), 7.52 (1H, t, J=8Hz), 7.77 (1H, br peak), 7.87 (1H, d, J=8Hz), 7.95 (1H, d, J=8Hz)

5

20) 2-Methylthio-1H-benzimidazole-4-carboxylic acid

NMR (DMSO-d<sub>6</sub>, δ) : 2.68 (3H, s), 7.22 (1H, t, J=8Hz), 7.70 (1H, d, J=8Hz), 7.76 (1H, d, J=8Hz)

10 21) 2-Methylsulfonyl-1H-benzimidazole-4-carboxylic acid

NMR (DMSO-d<sub>6</sub>, δ) : 3.56 (3H, s), 7.50 (1H, t, J=8Hz), 8.01 (1H, d, J=8Hz), 8.09 (1H, br peak)

22) 2-Sulfamoyl-1H-benzimidazole-4-carboxylic acid

15 NMR (DMSO-d<sub>6</sub>, δ) : 7.46 (1H, t, J=8Hz), 7.89-8.02 (3H, m), 8.07 (1H, d, J=8Hz)

23) 2-Methyl-1H-pyrazolo[1,5-b][1,2,4]triazole-7-carboxylic acid

20 NMR (DMSO-d<sub>6</sub>, δ) : 2.43 (3H, s), 7.82 (1H, s)

24) 2-(4-Pyridyl)-1H-benzimidazole-4-carboxylic acid

25 NMR (DMSO-d<sub>6</sub>, δ) : 7.37 (1H, t, J=8Hz), 7.89 (1H, d, J=8Hz), 8.00 (1H, d, J=8Hz), 8.27 (1H, d, J=6Hz), 8.74 (1H, d, J=6Hz)

25) 2-(3-Pyridyl)-1H-benzimidazole-4-carboxylic acid

30 NMR (DMSO-d<sub>6</sub>, δ) : 7.40 (1H, t, J=8Hz), 7.72 (1H, t, J=8Hz), 7.90 (1H, d, J=8Hz), 8.01 (1H, d, J=8Hz), 8.77-8.80 (2H, m), 9.52 (1H, s)

26) 2-(2-Pyridyl)-1H-benzimidazole-4-carboxylic acid

35 NMR (DMSO-d<sub>6</sub>, δ) : 7.39 (1H, t, J=8Hz), 7.57 (1H, t, J=7Hz), 7.87 (1H, d, J=8Hz), 7.98-8.06 (2H, m), 8.35 (1H, d, J=8Hz), 8.79 (1H, d, J=4Hz)

- 27) 2-Dimethylaminomethyl-1H-benzimidazole-4-carboxylic acid  
NMR (DMSO-d<sub>6</sub>, δ) : 2.89 (6H, s), 4.68 (2H, s), 7.39  
(1H, t, J=8Hz), 7.90 (1H, d, J=8Hz), 8.00 (1H, d,  
J=8Hz)
- 5
- 28) 2-(4-Methylpiperazin-1-yl)methyl-1H-benzimidazole-4-  
carboxylic acid  
NMR (DMSO-d<sub>6</sub>, δ) : 2.50 (3H, s), 2.72 (4H, br s), 2.88  
(4H, br s), 3.87 (2H, s), 7.27 (1H, t, J=8Hz), 7.77  
10 (1H, d, J=8Hz), 7.82 (1H, d, J=8Hz)
- 29) 2-(4-Dimethylaminopiperidino)methyl-1H-benzimidazole-4-  
carboxylic acid  
NMR (DMSO-d<sub>6</sub>, δ) : 1.90 (2H, br s), 2.10-2.20 (2H, m),  
15 2.52-2.70 (7H, m), 3.15-3.50 (6H, m), 7.30 (1H, t,  
J=8Hz), 7.82 (1H, d, J=8Hz), 7.90 (1H, d, J=8Hz)
- 30) 2-Morpholinomethyl-1H-benzimidazole-4-carboxylic acid  
NMR (DMSO-d<sub>6</sub>, δ) : 2.50 (4H, br s), 3.88 (4H, br s),  
20 4.72 (2H, s), 7.40 (1H, t, J=8Hz), 7.90 (1H, d,  
J=8Hz), 7.99 (1H, d, J=8Hz)
- 31) 2H-1,4-Benzoxazin-3-one-8-carboxylic acid  
NMR (DMSO-d<sub>6</sub>, δ) : 4.62 (2H, s), 6.96-7.05 (2H, m),  
25 7.30 (1H, d, J=8Hz)

#### Preparation 45

The following compounds were obtained according to a  
similar manner to that of Preparation 25.

- 30
- 1) 4-Amino-3-methoxy-N-methyl-N-[2-(5-tert-butoxycarbonyl-  
aminopent-1-yl)oxy-4-methyl]phenylbenzamide  
NMR (CDCl<sub>3</sub>, δ) : 1.42 (9H, s), 1.42-1.59 (4H, m), 1.70-  
1.81 (2H, m), 2.28 (9H, s), 3.06-3.17 (2H, m), 3.31  
35 (3H, s), 3.61 (3H, s), 3.76-3.93 (2H, m), 3.87 (2H,

s), 4.69 (1H, br), 6.43 (1H, d, J=8Hz), 6.57-6.63 (2H, m), 6.80-6.85 (2H, m), 6.89 (1H, d, J=8Hz)

2) tert-Butyl 4-amino-1H-benzimidazole-1-carboxylate

5 NMR (CDCl<sub>3</sub>, δ) : 1.68 (9H, s), 4.37 (2H, s), 6.61 (1H, d, J=8Hz), 7.16 (1H, dd, J=8, 8Hz), 7.32 (1H, d, J=8Hz), 8.30 (1H, s)

3) 2-[4,4-Dimethyl(2,5-oxazolinyl)]phenylamine

10 NMR (CDCl<sub>3</sub>, δ) : 1.39 (6H, s), 4.00 (2H, s), 6.06-6.28 (2H, br), 6.60-6.73 (2H, m), 7.19 (1H, m), 7.68 (1H, d, J=8Hz)

4) 4-Amino-N-[2-[4,4-dimethyl(2,5-oxazolinyl)]phenyl]-N-methyl-3-methoxybenzamide

15 NMR (CDCl<sub>3</sub>, δ) : 1.32 (6H, s), 3.38 (3H, s), 3.58 (3H, s), 3.86 (2H, br s), 4.07 (2H, s), 6.41 (1H, d, J=8Hz), 6.78-6.90 (2H, m), 7.12 (1H, d, J=8Hz), 7.22 (1H, dd, J=8, 8Hz), 7.35 (1H, dd, J=8, 8Hz),  
20 7.79 (1H, d, J=8Hz)

5) 4-Amino-3-methoxy-N-methyl-N-[2-(morpholin-4-yl)phenyl]benzamide

25 NMR (CDCl<sub>3</sub>, δ) : 2.52-2.68 (2H, m), 2.77-2.93 (2H, m), 3.46 (3H, s), 3.59 (3H, s), 3.63-3.82 (4H, m), 6.45 (1H, d, J=8Hz), 6.84 (1H, s), 6.86-6.96 (2H, m), 7.04 (1H, dd, J=8, 8Hz), 7.12-7.23 (2H, m)

6) 2-(4-Methyl-1-piperazinyl)phenylamine

30 NMR (CDCl<sub>3</sub>, δ) : 2.37 (3H, s), 2.46-2.75 (4H, m), 2.88-3.04 (4H, m), 3.94 (2H, br s), 6.75 (2H, dd, J=8, 8Hz), 6.92 (1H, dd, J=8, 8Hz), 7.02 (1H, d, J=8Hz)

7) 2-(2,5-Oxazolyl)phenylamine

35 NMR (CDCl<sub>3</sub>, δ) : 6.70-6.83 (2H, m), 7.16-7.28 (2H, m),

7.64 (1H, s), 7.86 (1H, m)

- 8) 2-(1-Aza-3-oxaspiro[4.4]non-1-en-2-yl)phenylamine

5 NMR (CDCl<sub>3</sub>, δ) : 1.52-2.06 (8H, m), 4.12 (2H, s), 6.10 (2H, br s), 6.59-6.73 (2H, m), 7.18 (1H, dd, J=8, 8Hz), 7.66 (1H, d, J=8Hz)

- 9) 4-Amino-2-methoxy-1H-benzimidazole

10 NMR (DMSO-d<sub>6</sub>, δ) : 4.01 (3H, s), 4.84 (2H, s), 6.30 (1H, d, J=8Hz), 6.47 (1H, br peak), 6.74 (1H, t, J=8Hz)

- 10) 4-Amino-2-[2-(dimethylamino)ethyl]-1H-benzimidazole

15 NMR (CDCl<sub>3</sub>, δ) : 2.39 (6H, s), 2.71 (2H, t, J=5Hz), 3.07 (2H, t, J=5Hz), 4.23 (2H, br peak), 6.50 (1H, d, J=8Hz), 6.84 (1H, d, J=8Hz), 7.00 (1H, t, J=8Hz)

- 11) 4-Amino-1-(tert-butoxycarbonyl)-2-[[2-[N-(tert-butoxycarbonyl)-N-methylamino]ethyl]amino]-1H-benzimidazole

20 NMR (CDCl<sub>3</sub>, δ) : 1.45 (9H, s), 1.69 (9H, s), 2.93 (3H, s), 3.51-3.65 (2H, m), 3.65-3.88 (2H, m), 6.57 (1H, d, J=8Hz), 6.88 (1H, t, J=8Hz), 7.02 (1H, d, J=8Hz)

- 12) 4-Amino-1-(tert-butoxycarbonyl)-2-[[2-[(tert-butoxycarbonylamino)ethyl]methylamino]-1H-benzimidazole

25 NMR (CDCl<sub>3</sub>, δ) : 1.35 (9H, s), 1.70 (9H, s), 3.03 (3H, s), 3.41-3.55 (2H, m), 3.61-3.77 (2H, m), 6.14 (1H, br peak), 6.59 (1H, d, J=8Hz), 6.91-7.10 (2H, m)

- 13) 4-Amino-1-(tert-butoxycarbonyl)-2-[[2-(dimethylamino)ethyl]amino]-1H-benzimidazole

30 NMR (CDCl<sub>3</sub>, δ) : 1.69 (9H, s), 2.43 (6H, br s), 2.80 (2H, br peak), 2.69-2.81 (2H, m), 6.56 (1H, d, J=8Hz), 6.85 (1H, t, J=8Hz), 7.06 (1H, d, J=8Hz)

35

14) 4-Amino-2-[[2-(dimethylamino)ethyl]methylamino]-1H-benzimidazole

NMR (DMSO-d<sub>6</sub>, δ) : 2.20 (6H, s), 2.45 (2H, t, J=5Hz),  
3.11 (3H, s), 3.52 (2H, t, J=5Hz), 6.18 (1H, d,  
J=8Hz), 6.44 (1H, d, J=8Hz), 6.60 (1H, t, J=8Hz)

#### Preparation 46

The following compounds were obtained according to a similar manner to that of Preparation 31.

1) Methyl-2-carbamoyl-1-(4-methoxybenzyl)-1H-benzimidazole-4-carboxylate

NMR (CDCl<sub>3</sub>, δ) : 3.74 (3H, s), 4.04 (3H, s), 5.65 (1H, br s), 5.98 (2H, s), 6.80 (2H, d, J=8Hz), 7.15 (1H, d, J=8Hz), 7.40 (1H, t, J=8Hz), 7.63 (1H, d, J=8Hz), 7.86 (1H, br s), 8.03 (1H, d, J=8Hz)

2) Methyl 2-(N,N-dimethylcarbamoyl)-1-(4-methoxybenzyl)-1H-benzimidazole-4-carboxylate

NMR (CDCl<sub>3</sub>, δ) : 3.10 (3H, s), 3.19 (3H, s), 3.76 (3H, s), 4.01 (3H, s), 5.54 (2H, s), 6.80 (2H, d, J=8Hz), 7.12 (2H, d, J=8Hz), 7.35 (1H, t, J=8Hz), 7.58 (1H, d, J=8Hz), 7.99 (1H, d, J=8Hz)

#### Preparation 47

The following compounds were obtained by using ethyl 2-phthalimidomethyl-1H-benzimidazole-4-carboxylate as a starting compound according to a similar manner to that of Preparation 31.

1) Ethyl 1-methyl-2-phthalimidomethyl-1H-benzimidazole-4-carboxylate

NMR (CDCl<sub>3</sub>, δ) : 1.26 (3H, t, J=7.5Hz), 3.95 (3H, s), 4.35 (2H, q, J=7.5Hz), 5.20 (2H, s), 7.32 (1H, t, J=8Hz), 7.52 (1H, d, J=8Hz), 7.70-7.80 (2H, m),

7.84-7.95 (3H, m)

2) Ethyl 3-methyl-2-phthalimidomethyl-3H-benzimidazole-4-carboxylate

5 NMR (CDCl<sub>3</sub>, δ) : 1.45 (3H, t, J=7.5Hz), 4.06 (3H, s),  
4.43 (2H, q, J=7.5Hz), 5.15 (2H, s), 7.21 (1H, t,  
J=8Hz), 7.71-7.80 (3H, m), 7.85 (1H, d, J=8Hz),  
7.87-7.94 (2H, m)

10 Preparation 48

To a solution of benzyl 2-tert-butyldiphenyl-silyloxymethylindole-4-carboxylate (805 mg) and N,N-dimethylaminopyridine (189 mg) in acetonitrile (15 ml) was added di-tert-butyl dicarbonate (507 mg) and the mixture  
15 was stirred at ambient temperature for 20 minutes. The resulting mixture was diluted with ethyl acetate (30 ml) and washed successively with saturated sodium bicarbonate aqueous solution and brine. The organic layer was dried over  
magnesium sulfate and concentrated in vacuo. The residue was  
20 purified by silica gel column chromatography (eluent; n-hexane:ethyl acetate = 15:1) to give benzyl 1-tert-butoxycarbonyl-2-tert-butyldiphenylsilyloxymethylindole-4-carboxylate (762 mg).

25 NMR (CDCl<sub>3</sub>, δ) : 1.12 (9H, s), 1.47 (9H, s), 5.01 (2H, s), 5.47 (2H, s), 7.27-7.50 (12H, m), 7.55 (1H, s), 7.71 (4H, d, J=8Hz), 8.01 (1H, d, J=8Hz), 8.39 (1H, d, J=8Hz)

Preparation 49

30 The following compounds were obtained according to a similar manner to that of Preparation 48.

1) Methyl 2-benzyloxymethyl-1-tert-butoxycarbonylindoline-4-carboxylate

35 NMR (CDCl<sub>3</sub>, δ) : 1.50 (9H, s), 3.42-3.53 (3H, m), 3.67

(1H, dd, J=4, 12Hz), 3.89 (3H, s), 4.50 (2H, s),  
4.56-4.67 (1H, br), 7.20-7.38 (7H, m), 7.60 (1H, d,  
J=8Hz)

- 5        2) Benzyl 1-tert-butoxycarbonyl-3-formylindole-4-  
         carboxylate

NMR (CDCl<sub>3</sub>, δ) : 1.68 (9H, s), 5.43 (2H, s), 7.32-7.49  
(6H, m), 7.92 (1H, d, J=8Hz), 8.37 (1H, s), 8.49  
(1H, d, J=8Hz), 10.47 (1H, s)

10

- 3) Benzyl 1-tert-butoxycarbonyl-2-formylindole-4-  
carboxylate

NMR (CDCl<sub>3</sub>, δ) : 1.72 (9H, s), 5.45 (2H, s), 7.34-7.45  
(3H, m), 7.47-7.57 (3H, m), 8.07 (1H, d, J=9Hz),  
8.10 (1H, s), 8.43 (1H, d, J=9Hz), 10.40 (1H, s)

15

- 4) Benzyl 1-tert-butoxycarbonyl-2-methylindole-4-  
carboxylate

NMR (CDCl<sub>3</sub>, δ) : 1.70 (9H, s), 2.61 (3H, s), 5.40 (2H,  
s), 7.07 (1H, s), 7.22-7.28 (1H, m), 7.31-7.43 (3H,  
m), 7.47-7.52 (2H, m), 7.97 (1H, d, J=8Hz), 8.35  
(1H, d, J=8Hz)

20

- 5) Benzyl 1-tert-butoxycarbonylindole-6-carboxylate

NMR (CDCl<sub>3</sub>, δ) : 1.67 (9H, s), 5.39 (2H, s), 6.61 (1H,  
d, J=3Hz), 7.32-7.42 (3H, m), 7.46-7.50 (2H, m),  
7.59 (1H, d, J=8Hz), 7.78 (1H, d, J=3Hz), 7.97 (1H,  
d, J=8Hz) 8.86 (1H, s)

25

- 30       6) 3-Methoxy-4-methoxycarbonyl-N-methyl-N-[4-methyl-2-[4-  
(tert-butoxycarbonylamino)but-1-yloxy]]phenylbenzamide

NMR (CDCl<sub>3</sub>, δ) : 1.42 (9H, s), 1.57-1.70 (2H, m), 1.72-  
1.86 (2H, m), 2.23 (3H, s), 3.19 (2H, t, J=7.5Hz),  
3.31 (3H, s), 3.69 (3H, s), 3.78-3.96 (2H, m), 3.82  
(3H, s), 6.55-6.60 (2H, m), 6.87 (1H, d, J=8Hz),

35

6.91 (1H, d, J=8Hz), 6.94 (1H, s), 7.57 (1H, d, J=8Hz)

7) tert-Butyl 4-nitro-1H-benzimidazole-1-carboxylate

5 NMR (CDCl<sub>3</sub>, δ) : 1.72 (9H, s), 7.53 (1H, dd, J=8, 8Hz),  
8.20 (1H, d, J=8Hz), 8.39 (1H, d, J=8Hz), 8.61 (1H, s)

8) 1-(tert-Butoxycarbonyl)-2-[[2-[N-(tert-butoxycarbonyl)-  
10 N-methylamino]ethyl]amino]-4-nitro-1H-benzimidazole

NMR (CDCl<sub>3</sub>, δ) : 1.41 (9H, s), 1.71 (9H, s), 2.95 (3H, s),  
3.60 (1H, t-like, J=5Hz), 3.84 (1H, q-like, J=5Hz), 7.04 (1H, t, J=8Hz), 7.31 (1H, d, J=8Hz),  
8.00 (1H, d, J=8Hz)

9) 1-(tert-Butoxycarbonyl)-2-[[2-[(tert-butoxy)carbonyl-  
amino]ethyl]methylamino]-4-nitro-1H-benzimidazole

15 NMR (CDCl<sub>3</sub>, δ) : 1.39 (9H, s), 1.69 (9H, s), 3.11 (3H, s),  
3.50 (2H, q-like, J=5Hz), 3.80 (2H, t-like, J=5Hz), 6.01 (1H, br peak), 7.11 (1H, t, J=8Hz),  
20 7.88 (1H, d, J=8Hz), 8.03 (1H, d, J=8Hz)

10) 1-(tert-Butoxycarbonyl)-2-[[2-(dimethylamino)ethyl]-  
amino]-4-nitro-1H-benzimidazole

25 NMR (CDCl<sub>3</sub>, δ) : 1.72 (9H, s), 2.55 (6H, br peak), 3.00 (2H, br peak),  
3.92 (2H, br peak), 7.07 (1H, t, J=8Hz), 7.84 (1H, br peak), 7.90 (1H, d, J=8Hz),  
8.01 (1H, d, J=8Hz)

30 Preparation 50

The following compounds were obtained according to a similar manner to that of Example 1.

1) 3-Methoxy-4-methoxycarbonyl-N-methyl-N-(4-methyl-2-  
35 nitrophenyl)benzamide



NMR (CDCl<sub>3</sub>, δ) : 2.35 (3H, s), 3.37 (3H, s), 3.70 (3H, s), 3.80 (3H, s), 6.80 (1H, d, J=8Hz), 6.91 (1H, s), 7.11 (1H, d, J=8Hz), 7.30 (1H, d, J=8Hz), 7.54 (1H, d, J=8Hz), 7.63 (1H, s)

5

- 2) 3-Methoxy-4-methoxycarbonyl-N-[4-methyl-2-(4-phthalimidobut-1-yloxy)]phenylbenzamide

NMR (CDCl<sub>3</sub>, δ) : 1.87-1.96 (4H, m), 2.31 (3H, s), 3.78 (2H, m), 3.91 (3H, s), 3.98 (3H, s), 4.10 (2H, m), 6.70 (1H, s), 6.79 (1H, d, J=8Hz), 7.35 (1H, d, J=8Hz), 7.62 (1H, s), 7.66-7.74 (2H, m), 7.79-7.87 (2H, m), 7.96 (1H, d, J=8Hz), 8.33 (1H, d, J=8Hz), 8.52 (1H, s)

10

- 3) 3-Methoxy-4-nitro-N-[4-methyl-2-(5-phthalimidopent-1-yloxy)]phenylbenzamide

NMR (CDCl<sub>3</sub>, δ) : 1.48-1.60 (2H, m), 1.70-1.82 (2H, m), 1.85-1.95 (2H, m), 2.31 (3H, s), 3.69 (2H, t, J=7.5Hz), 4.02 (3H, s), 4.04 (2H, t, J=7.5Hz), 6.71 (1H, s), 6.81 (1H, d, J=8Hz), 7.39 (1H, d, J=8Hz), 7.66-7.72 (2H, m), 7.76-7.74 (2H, m), 7.98 (1H, d, J=8Hz), 8.32 (1H, d, J=8Hz), 8.52 (1H, s)

20

#### Preparation 51

The following compounds were obtained according to a similar manner to that of Example 7.

- 1) 4-Amino-2-phthalimidomethyl-1H-benzimidazole

NMR (DMSO-d<sub>6</sub>, δ) : 4.95 (2H, s), 5.10 (2H, br s), 6.30 (1H, d, J=8Hz), 6.57 (1H, d, J=8Hz), 6.82 (1H, t, J=8Hz), 7.83-8.02 (4H, m)

30

- 2) 4-Amino-2-(2-phthalimidoethyl)-1H-benzimidazole

NMR (DMSO-d<sub>6</sub>, δ) : 3.11 (2H, br peak), 4.00 (2H, br peak), 5.01 (2H, br peak), 6.28 (1H, br peak), 6.60

35

(1H, br peak), 6.80 (1H, br peak), 7.85 (4H, br peak)

- 3) 4-Amino-2-tert-butyl-diphenylsiloxymethyl-1H-benzimidazole

NMR (CD<sub>3</sub>OD,  $\delta$ ) : 1.09 (9H, s), 4.91 (2H, s), 6.53 (1H, d, J=8Hz), 6.88 (1H, d, J=8Hz), 6.99 (1H, t, J=8Hz), 7.32-7.50 (6H, m), 7.66-7.75 (4H, m)

- 4) 4-Amino-2-[(tert-butoxy)carbonylamino]-1H-benzimidazole

NMR (CDCl<sub>3</sub>,  $\delta$ ) : 1.69 (9H, s), 6.58 (1H, d, J=8Hz), 6.90 (1H, t, J=8Hz), 7.06 (1H, d, J=8Hz)

- 5) 4-Amino-2-[(methylsulfonyl)amino]-1H-benzimidazole

NMR (DMSO-d<sub>6</sub>,  $\delta$ ) : 3.40 (3H, s), 4.90 (2H, s), 6.41-6.51 (1H, m), 6.65 (2H, s), 6.71-6.81 (2H, m)

- 6) 4-Amino-2-methoxymethyl-1H-benzimidazole

NMR (DMSO-d<sub>6</sub>,  $\delta$ ) : 3.32 (3H x 2/3, s), 3.37 (3H x 1/3, s), 4.55 (2H x 2/3, s), 4.60 (2H x 1/3, s), 5.65 (2H, s), 6.26-6.40 (1H, m), 6.62 (1H x 2/3, d, J=8Hz), 6.73-6.90 (1H + 1H x 1/3, m)

- 7) 4-Amino-2-(n-propyl)-1H-benzimidazole

NMR (CDCl<sub>3</sub>,  $\delta$ ) : 1.00 (3H, t, J=7.5Hz), 1.83 (2H, m), 2.86 (2H, t, J=7.5Hz), 4.26 (2H, br s), 6.50 (1H, d, J=8Hz), 6.80 (1H, d, J=8Hz), 7.00 (1H, t, J=8Hz)

- 8) 4-Amino-2-isopropyl-1H-benzimidazole

NMR (CDCl<sub>3</sub>,  $\delta$ ) : 1.43 (6H, d, J=7.5Hz), 3.23 (1H, m), 4.28 (1H, br s), 6.50 (1H, d, J=8Hz), 6.80 (1H, br peak), 7.01 (1H, t, J=8Hz), 8.84 (1H, br s)

- 9) 4-Amino-2-(3-pyridyl)-1H-benzimidazole

NMR (DMSO-d<sub>6</sub>,  $\delta$ ) : 5.30 (2H, br s), 6.38 (1H, d,

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J=8Hz), 6.73 (1H, d, J=8Hz), 6.93 (1H, t, J=8Hz), 7.56 (1H, dd, J=5, 8Hz), 8.43 (1H, d, J=8Hz), 8.93 (1H, d, J=5Hz), 9.30 (1H, s)

- 5 10) 4-Amino-2-(N,N-dimethylaminomethyl)-1H-benzimidazole

NMR (CDCl<sub>3</sub>, δ) : 2.41 (6H, s), 3.83 (2H, s), 6.50 (1H, d, J=8Hz), 6.83 (1H, d, J=8Hz), 7.04 (1H, t, J=8Hz)

- 10      11) 4-Amino-2-(1-imidazolyl)methyl-1H-benzimidazole

NMR (DMSO-d<sub>6</sub>, δ) : 5.16 (2H, s), 5.38 (2H, s), 6.33 (1H, d, J=8Hz), 6.67 (1H, d, J=8Hz), 6.86 (1H, t, J=8Hz), 6.91 (1H, s), 7.23 (1H, s), 7.77 (1H, s)

- 15 12) 4-Amino-2-[(4-methylpiperazin-1-yl)methyl]-1H-  
benzimidazole

NMR (DMSO-d<sub>6</sub>, δ) : 2.15 (3H, s), 2.20-2.49 (8H, m),  
3.61 (2H x 2/3, s), 3.65 (2H x 1/3, s), 5.10 (2H x  
2/3, s), 5.20 (2H x 1/3, s), 6.28 (1H x 2/3, d,  
J=8Hz), 6.33 (1H x 1/3, d, J=8Hz), 6.60 (1H x 2/3,  
d, J=8Hz), 6.73-6.86 (1H + 1H x 1/3, m)

- 13) 4-Amino-2-(morpholin-4-ylmethyl)-1H-benzimidazole

NMR (CDCl<sub>3</sub>,  $\delta$ ) : 2.50-2.60 (4H, m), 3.68-3.76 (4H, m), 3.79 (2H, s), 4.28 (2H, br peak), 6.51 (1H, d, J=8Hz), 6.83 (1H, d, J=8Hz), 7.03 (1H, t, J=8Hz)

- 14) 4-Amino-2-(pyrrolidin-1-ylmethyl)-1H-benzimidazole

NMR (CDCl<sub>3</sub>, δ) : 1.83-2.00 (2H, m), 2.71-2.83 (2H, m),  
4.03 (2H, s), 6.50 (1H, d, J=8Hz), 6.85 (1H, d,  
J=8Hz), 7.03 (1H, t, J=8Hz)

- 15) 4-Amino-2-(piperidinomethyl)-1H-benzimidazole

NMR (CDCl<sub>3</sub>, δ) : 1.47-1.63 (2H, m), 1.73-1.86 (4H, m),  
2.73 (4H, br peak), 4.01 (2H, s), 4.26 (2H, br

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peak), 6.51 (1H, d, J=8Hz), 6.90 (1H, d, J=8Hz),  
7.05 (1H, t, J=8Hz)

- 5 16) 4-Amino-2-[2-(4-methylpiperazin-1-yl)ethyl]-1H-benzimidazole

NMR (DMSO-d<sub>6</sub>, δ) : 2.18 (3H, s), 2.22-2.53 (8H, m),  
2.72 (2H, t, J=7.5Hz), 2.91 (2H, t, J=7.5Hz), 5.02  
(2H, br peak), 6.29 (1H, d, J=8Hz), 6.61 (1H, d,  
J=8Hz), 6.80 (1H, t, J=8Hz)

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- 17) 4-Amino-2-(4-methylpiperazin-1-yl)-1H-benzimidazole

NMR (DMSO-d<sub>6</sub>, δ) : 2.22 (3H, s), 2.36-2.46 (4H, m),  
3.36-3.49 (4H, m), 4.70 (2H x 2/3, br s), 4.82 (2H  
x 1/3, br s), 6.20 (1H x 1/3, d, J=8Hz), 6.23 (1H x  
2/3, d, J=8Hz), 6.45 (1H x 2/3, d, J=8Hz), 6.52 (1H  
x 1/3, d, J=8Hz), 6.62 (1H x 2/3, t, J=8Hz), 6.68  
(1H x 1/3, t, J=8Hz)

15

- 18) 4-Amino-2-dimethylamino-1H-benzimidazole

NMR (DMSO-d<sub>6</sub>, δ) : 3.21 (6H, s), 5.73 (2H, br peak),  
6.46 (1H, d, J=8Hz), 6.57 (1H, d, J=8Hz), 6.93 (1H,  
t, J=8Hz)

20

- 19) 4-Amino-2-(1-imidazolyl)-1H-benzimidazole

NMR (DMSO-d<sub>6</sub>, δ) : 5.20 (2H, br s), 6.42 (1H, d,  
J=8Hz), 6.72 (1H, br peak), 6.94 (1H, t, J=8Hz),  
7.20 (1H, s), 7.85 (1H, s), 8.40 (1H, s)

25

- 20) 4-Amino-2-(1,2,4-tetrazol-1-yl)-1H-benzimidazole

NMR (DMSO-d<sub>6</sub>, δ) : 5.31 (2H, br peak), 6.43 (1H, d,  
J=8Hz), 6.85 (1H, br peak), 6.95 (1H, t, J=8Hz),  
8.42 (1H, s), 9.34 (1H, s)

30

- 21) 4-Amino-2-[(2-methoxyethyl)amino]-1H-benzimidazole

NMR (DMSO-d<sub>6</sub>, δ) : 3.30 (3H, s), 3.45-3.60 (4H, m),

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143

6.32 (1H, d, J=8Hz), 6.50 (1H, d, J=8Hz), 6.75 (1H, t, J=8Hz), 7.55 (1H, br peak)

#### Preparation 52

5       The following compound was obtained according to a similar manner to that of Example 14.

Methyl 2-formyl-1H-benzimidazole-4-carboxylate

10       NMR (DMSO-d<sub>6</sub>, δ) : 3.97 (3H, s), 7.50 (1H, t, J=8Hz),  
8.03 (1H, d, J=8Hz), 8.11 (1H, d, J=8Hz), 10.06 (1H, s)

#### Preparation 53

15       The following compound was obtained according to a similar manner to that of Example 16.

2-Methoxymethyl-4-nitro-1H-benzimidazole

20       NMR (CDCl<sub>3</sub>, δ) : 3.59 (3H, s), 4.85 (2H, s), 7.40 (1H, t, J=8Hz), 8.08 (1H, d, J=8Hz), 8.18 (1H, d, J=8Hz)

#### Preparation 54

25       To a solution of ethyl 2,3-diaminobenzoate (4.72 g) and pyridine (2.49 g) in dichloroethane (50 ml) was added chloroacetyl chloride (3.11 g) in chloroform (10 ml) at -70°C and the reaction mixture was stood overnight. After the reaction mixture was concentrated in vacuo, the residue was diluted with ethanol (50 ml). To the solution was added p-toluenesulfonic acid (249 mg) and the reaction mixture was refluxed for 2 hours. After the reaction mixture was concentrated in vacuo, the residue was diluted with ethyl acetate and saturated sodium hydrogen carbonate aqueous solution. The organic layer was separated and washed with brine. The solution was dried over magnesium sulfate and concentrated in vacuo. The residue was purified by silica gel column chromatography (n-hexane:ethyl acetate = 4:1) to

30

35

give ethyl 2-chloromethyl-1H-benzimidazole-4-carboxylate  
(2.98 g).

NMR (CDCl<sub>3</sub>,  $\delta$ ) : 0.94 (3H, t, J=7Hz), 4.47 (2H, q,  
J=7Hz), 4.86 (2H, s), 7.32 (1H, t, J=8Hz), 7.93  
(2H, d, J=8Hz)

#### Preparation 55

The following compounds were obtained according to a  
similar manner to that of Preparation 54.

1) 4-Nitro-2-(n-propyl)-1H-benzimidazole

NMR (CDCl<sub>3</sub>,  $\delta$ ) : 1.08 (3H, t, J=7.5Hz), 1.94 (2H, m),  
2.99 (2H, t, J=7.5Hz), 7.34 (1H, t, J=8Hz), 8.03  
(1H, d, J=8Hz), 8.13 (1H, d, J=8Hz)

2) 2-Isopropyl-4-nitro-1H-benzimidazole

NMR (CDCl<sub>3</sub>,  $\delta$ ) : 1.51 (6H, d, J=7.5Hz), 3.32 (1H, m),  
7.34 (1H, t, J=8Hz), 8.06 (1H, d, J=8Hz), 8.12 (1H,  
d, J=8Hz)

3) 4-Nitro-2-(3-pyridyl)-1H-benzimidazole

NMR (DMSO-d<sub>6</sub>,  $\delta$ ) : 7.47 (1H, t, J=8Hz), 7.63 (1H, dd,  
J=5, 8Hz), 8.17 (2H, d, J=8Hz), 8.69 (1H, dd, J=8,  
2Hz), 8.74 (1H, dd, J=5, 2Hz), 9.47 (1H, d, J=2Hz)

4) 2-(2-Chloroethyl)-4-nitro-1H-benzimidazole

NMR (CDCl<sub>3</sub>,  $\delta$ ) : 3.49 (2H, t, J=7Hz), 4.04 (2H, t,  
J=7Hz), 7.39 (1H, t, J=8Hz), 8.06 (1H, d, J=8Hz),  
8.17 (1H, d, J=8Hz)

5) Ethyl 2-(3-pyridyl)-1H-benzimidazole-4-carboxylate

NMR (CDCl<sub>3</sub>,  $\delta$ ) : 1.47 (3H, t, J=7Hz), 4.48 (3H, q,  
J=7Hz), 7.36 (1H, t, J=8Hz), 7.46-7.50 (1H, m),  
7.93 (1H, d, J=8Hz), 8.03 (1H, d, J=8Hz), 8.42 (1H,  
d, J=8Hz), 8.73 (1H, d, J=3Hz), 9.32 (1H, s)

- 6) Ethyl 2-(2-pyridyl)-1H-benzimidazole-4-carboxylate .  
NMR (CDCl<sub>3</sub>, δ) : 1.48 (3H, t, J=7Hz), 4.50 (2H, q,  
J=7Hz), 7.31-7.40 (2H, m), 7.86 (1H, t, J=8Hz),  
7.97 (1H, d, J=8Hz), 8.03 (1H, d, J=8Hz), 8.40 (1H,  
5 d, J=8Hz), 8.68 (1H, d, J=3Hz)

#### Preparation 56

The following compounds were obtained according to a  
similar manner to that of Example 26.

10

- 1) 3-Methoxy-4-methoxycarbonyl-N-methyl-N-[4-methyl-2-(4-aminobut-1-yloxy)]phenylbenzamide

15

- 2) 3-Methoxy-N-methyl-4-nitro-N-[2-(5-tert-butoxycarbonyl-aminopent-1-yl)oxy-4-methyl]phenylbenzamide

20

NMR (CDCl<sub>3</sub>, δ) : 1.44 (9H, s), 1.47-1.68 (4H, m), 1.73-1.87 (2H, m), 2.29 (3H, s), 3.10-3.18 (2H, m), 3.31 (3H, s), 3.79 (3H, s), 3.84-3.95 (2H, m), 6.58-6.62 (2H, m), 6.88 (1H, d, J=8Hz), 6.95 (1H, d, J=8Hz),  
7.09 (1H, s), 7.62 (1H, d, J=8Hz)

25

- 3) Ethyl 2-aminomethyl-1-methyl-1H-benzimidazole-4-carboxylate

NMR (CDCl<sub>3</sub>, δ) : 1.45 (3H, t, J=7.5Hz), 3.84 (3H, s),  
4.20 (2H, s), 4.49 (2H, q, J=7.5Hz), 7.31 (1H, t, J=8Hz), 7.51 (1H, d, J=8Hz), 7.93 (1H, d, J=8Hz)

30

- 4) Ethyl 2-aminomethyl-3-methyl-3H-benzimidazole-4-carboxylate

NMR (CDCl<sub>3</sub>, δ) : 1.43 (3H, t, J=7.5Hz), 3.93 (3H, s),  
4.15 (2H, s), 4.43 (2H, q, J=7.5Hz), 7.25 (1H, t, J=8Hz), 7.76 (1H, d, J=8Hz), 7.90 (1H, d, J=8Hz)

#### Preparation 57

35

The following compounds were obtained according to a

similar manner to that of Example 30.

1) Methyl 2-carbamoyl-1H-benzimidazole-4-carboxylate

5 NMR (DMSO-d<sub>6</sub>, δ) : 3.94 (3H, s), 7.36 (1H, t, J=8Hz),  
7.82-7.92 (2H, m), 7.97 (1H, d, J=8Hz), 8.26 (1H,  
br s)

2) Methyl 2-(N,N-dimethylcarbamoyl)-1H-benzimidazole-4-carboxylate

10 NMR (CDCl<sub>3</sub>, δ) : 3.21 (3H, s), 3.80 (3H, s), 4.02 (3H,  
s), 7.38 (1H, t, J=8Hz), 8.04 (2H, d, J=8Hz)

3) 2-(N,N-Dimethylcarbamoyl)-4-nitro-1H-benzimidazole

15 NMR (DMSO-d<sub>6</sub>, δ) : 3.10 (3H, s), 3.33 (3H, s), 7.51  
(3H, t, J=8Hz), 8.09-8.25 (2H, m)

Preparation 58

To a suspension of 3-formylindole-4-carboxylic acid (390 mg) and potassium carbonate (285 mg) in N,N-dimethylformamide (10 ml) was added benzyl bromide (353 mg) at ambient temperature and the mixture was stirred for 4 hours. The resulting mixture was diluted with ethyl acetate and water, then the layers were separated. The organic layer was washed with brine, dried over magnesium sulfate and concentrated in vacuo. The residual solid was triturated with diethyl ether:n-hexane (1:6) to give benzyl 3-formylindole-4-carboxylate (520 mg).

20 NMR (DMSO-d<sub>6</sub>, δ) : 5.37 (2H, s), 7.28-7.48 (7H, m),  
7.62 (1H, d, J=8Hz), 7.75 (1H, d, J=8Hz), 8.36 (1H,  
30 s), 10.22 (1H, s)

Preparation 59

The following compounds were obtained according to a similar manner to that of Preparation 58.



## 1) Benzyl 2-hydroxymethylindole-4-carboxylate

NMR (CDCl<sub>3</sub>, δ) : 4.88 (1H, d, J=6Hz), 5.44 (2H, s),  
7.03 (1H, s), 7.22 (1H, t, J=8Hz), 7.32-7.43 (3H,  
m), 7.47-7.52 (2H, m), 7.56 (1H, d, J=8Hz), 7.94  
(1H, d, J=8Hz), 8.52-8.58 (1H, br)

## 2) Benzyl 2-methylindole-4-carboxylate

NMR (CDCl<sub>3</sub>, δ) : 2.48 (3H, s), 5.44 (2H, s), 6.88 (1H,  
s), 7.13 (1H, t, J=8Hz), 7.30-7.52 (6H, m), 7.90  
(1H, d, J=8Hz), 8.03-8.10 (1H, br)

Preparation 60

To a solution of benzyl 1-tert-butoxycarbonyl-3-  
formylindole-4-carboxylate (363 mg) in methanol (15 ml) was  
added sodium borohydride (109 mg) at 0°C and the mixture was  
stirred for 5 minutes. The resulting mixture was diluted  
with water and the solution was neutralized with 1N  
hydrochloric acid. The solution was extracted with ethyl  
acetate, and then the organic solution was washed  
successively with saturated sodium bicarbonate aqueous  
solution and brine, dried over magnesium sulfate and  
concentrated in vacuo to afford benzyl 1-tert-butoxycarbonyl-  
3-hydroxymethylindole-4-carboxylate (365 mg).

NMR (CDCl<sub>3</sub>, δ) : 1.67 (9H, s), 4.11 (1H, t, J=8Hz),  
4.72 (2H, d, J=8Hz), 5.43 (2H, s), 7.30-7.51 (6H,  
m), 7.71 (1H, s), 7.92 (1H, d, J=8Hz), 8.49 (1H, d,  
J=8Hz)

Preparation 61

The following compound was obtained according to a  
similar manner to that of Preparation 60.

Benzyl 1-tert-butoxycarbonyl-2-hydroxymethylindole-4-  
carboxylate

NMR (CDCl<sub>3</sub>, δ) : 1.73 (9H, s), 3.58 (1H, t, J=9Hz),

148

4.82 (2H, d, J=9Hz), 5.42 (2H, s), 7.30-7.42 (5H, m), 7.47-7.50 (2H, m), 8.00 (1H, d, J=8Hz), 8.22 (1H, d, J=8Hz)

5 Preparation 62

To a solution of 3-methoxy-4-methoxycarbonylbenzoic acid (800 mg) in dichloromethane (15 ml) was added oxalyl chloride (0.664 ml) and 1 drop of N,N-dimethylformamide and the mixture was stirred at ambient temperature for 2 hours.

10 After being removed a solvent by evaporation, residual acid chloride in dichloromethane (5 ml) was added to a mixture of 2-[4,4-dimethyl(2,5-oxazolinyl)]phenylamine (724 mg) and triethylamine (770 mg) in dichloromethane (15 ml) at 0°C and the mixture was stirred at ambient temperature for 2 hours.

15 After being removed a solvent by evaporation, the residue was diluted with ethyl acetate and washed successively with 1N hydrochloric acid, saturated aqueous sodium hydrogencarbonate and brine and dried over sodium sulfate. The solvent was removed by rotary evaporation to give N-[2-[4,4-dimethyl(2,5-oxazolinyl)]phenyl]-3-methoxy-4-methoxycarbonylbenzamide (1.46 g).

20 NMR (CDCl<sub>3</sub>, δ) : 1.44 (6H, s), 3.94 (3H, s), 4.01 (3H, s), 4.12 (3H, s), 7.16 (1H, dd, J=8, 8Hz), 7.53 (1H, dd, J=8, 8Hz), 7.72 (1H, d, J=8Hz), 7.78 (1H, s), 7.85-7.94 (2H, m), 8.92 (1H, d, J=8Hz)

Preparation 63

The following compounds were obtained according to a similar manner to that of Preparation 62.

30

1) N-[2-[4,4-Dimethyl(2,5-oxazolinyl)]phenyl]-3-methoxy-4-nitrobenzamide

35 NMR (CDCl<sub>3</sub>, δ) : 1.43 (6H, s), 4.08 (3H, s), 4.13 (2H, s), 7.18 (1H, dd, J=8, 8Hz), 7.56 (1H, dd, J=8, 8Hz), 7.78 (1H, d, J=8Hz), 7.86-8.00 (3H, m), 8.91

(1H, d, J=8Hz)

- 2) 3-Methoxy-4-methoxycarbonyl-N-[2-(morpholin-4-yl)phenyl]benzamide

5 NMR (CDCl<sub>3</sub>, δ) : 2.87-2.98 (4H, m), 3.82-3.90 (4H, m),  
3.91 (3H, s), 4.00 (3H, s), 7.09-7.18 (1H, m),  
7.20-7.30 (1H, m), 7.39 (1H, d, J=8Hz), 7.66 (1H,  
s), 7.92 (1H, d, J=8Hz), 8.54 (1H, d, J=8Hz), 9.58  
(1H, s)

10

- 3) 3-Methoxy-N-[2-(morpholin-4-yl)phenyl]-4-nitrobenzamide

NMR (CDCl<sub>3</sub>, δ) : 2.88-3.08 (4H, br), 3.82-3.99 (4H,  
br), 4.08 (3H, s), 7.12-7.36 (3H, m), 7.46 (1H, m),  
7.82 (1H, s), 7.97 (1H, d, J=8Hz), 8.48 (1H, m)

15

- 4) 3-Methoxy-4-methoxycarbonyl-N-[2-(1-pyrrolyl)phenyl]-benzamide

20 NMR (CDCl<sub>3</sub>, δ) : 3.90 (3H, s), 3.92 (3H, s), 6.42-6.49  
(2H, m), 6.82-6.90 (2H, m), 7.04-7.12 (1H, m),  
7.18-7.32 (2H, m), 7.39 (1H, d, J=8Hz), 7.48 (1H,  
dd, J=8, 8Hz), 7.70-7.83 (2H, m), 8.62 (1H, d,  
J=8Hz)

- 5) 3-Methoxy-4-methoxycarbonyl-N-(2-piperidinophenyl)-benzamide

25

NMR (CDCl<sub>3</sub>, δ) : 1.54-1.81 (6H, m), 2.79-2.90 (4H, m),  
3.92 (3H, s), 4.01 (3H, s), 7.04-7.15 (1H, m), 7.20  
(1H, dd, J=8, 8Hz), 7.42 (1H, d, J=8Hz), 7.66 (3H,  
s), 7.93 (1H, d, J=8Hz), 8.54 (1H, d, J=8Hz), 9.68  
(1H, s)

30

- 6) 3-Methoxy-4-nitro-N-(2-piperidinophenyl)benzamide

35 NMR (CDCl<sub>3</sub>, δ) : 1.56-1.82 (6H, m), 2.78-2.92 (4H, m),  
4.06 (3H, s), 7.08-7.29 (3H, m), 7.44 (1H, m), 7.77  
(1H, s), 7.97 (1H, d, J=8Hz), 8.51 (1H, d, J=8Hz),

150

9.71 (1H, s)

- 7) 3-Methoxy-4-methoxycarbonyl-N-[2-(4-methyl-1-piperazinyl)phenyl]benzamide

5 NMR (CDCl<sub>3</sub>, δ) : 2.38 (3H, s), 2.48-2.79 (4H, br),  
2.91-3.02 (4H, m), 3.94 (3H, s), 4.02 (3H, s), 7.11  
(1H, dd, J=8, 8Hz), 7.18-7.30 (2H, m), 7.42 (1H, d,  
J=8Hz), 7.65 (1H, s), 7.92 (1H, d, J=8Hz), 8.54  
(1H, d, J=8Hz), 9.58 (1H, s)

10

- 8) 3-Methoxy-N-[2-(4-methyl-1-piperazinyl)phenyl]-4-nitrobenzamide

NMR (CDCl<sub>3</sub>, δ) : 2.42 (3H, s), 2.53-2.80 (4H, m), 2.92-  
3.06 (4H, m), 4.07 (3H, s), 7.11-7.20 (1H, m),  
15 7.21-7.32 (2H, m), 7.45 (1H, m), 7.79 (1H, s), 7.98  
(1H, d, J=8Hz), 8.52 (1H, d, J=8Hz)

- 9) 3-Methoxy-4-methoxycarbonyl-N-[2-(2,5-oxazolyl)phenyl]-benzamide

20 NMR (CDCl<sub>3</sub>, δ) : 1.63 (1H, br s), 3.94 (3H, s), 4.04  
(3H, s), 7.22 (1H, dd, J=8, 8Hz), 7.31 (1H, s),  
7.53 (1H, m), 7.72-7.82 (3H, m), 7.94 (1H, d,  
J=8Hz), 8.09 (1H, m), 8.98 (1H, d, J=8Hz)

- 25 10) 3-Methoxy-4-methoxycarbonyl-N-[2-(2,5-oxazolinyl)-phenyl]benzamide

NMR (CDCl<sub>3</sub>, δ): 3.92 (3H, s), 4.02 (3H, s), 4.20 (9H, t,  
J=8Hz), 4.44 (9H, t, J=8Hz), 7.14 (1H, dd, J=8, 8Hz),  
7.54 (1H, dd, J=8, 8Hz), 7.69 (1H, d, J=8Hz), 7.75  
30 (1H, s), 7.87-7.96 (2H, m), 8.95 (1H, d, J=8Hz)

- 11) 3-Methoxy-4-methoxycarbonyl-N-[2-(3H,4H,5H-2,6-oxazinyl)phenyl]benzamide

NMR (CDCl<sub>3</sub>, δ) : 1.98-2.11 (2H, m), 3.71 (2H, t,  
J=7Hz), 3.93 (3H, s), 4.00 (3H, s), 4.43 (2H, t,

35

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J=7Hz), 7.09 (1H, dd, J=8, 8Hz), 7.47 (1H, dd, J=8, 8Hz), 7.56 (1H, d, J=8Hz), 7.70 (1H, s), 7.89 (1H, d, J=8Hz), 7.93 (1H, d, J=8Hz), 8.89 (1H, d, J=8Hz)

- 5 12) N-[2-(1-Aza-3-oxaspiro[4.4]non-1-en-2-yl)phenyl]-3-methoxy-4-methoxycarbonylbenzamide

NMR (CDCl<sub>3</sub>, δ) : 1.70-1.84 (4H, m), 1.85-2.09 (4H, m),  
3.93 (3H, s), 4.00 (3H, s), 4.26 (2H, s), 7.15 (1H,  
10 dd, J=8, 8Hz), 7.52 (1H, dd, J=8, 8Hz), 7.69 (1H,  
d, J=8Hz), 7.77 (1H, s), 7.84 (1H, d, J=8Hz), 7.91  
(1H, d, J=8Hz), 8.94 (1H, d, J=8Hz)

#### Preparation 64

To a solution of N-[2-[4,4-dimethyl(2,5-oxazolinyl)]-  
15 phenyl]-3-methoxy-4-methoxycarbonylbenzamide (1.45 g) in  
N,N-dimethylformamide (18 ml) was added portionwise sodium  
hydride (167 mg) at 0°C and the mixture was stirred at 0°C  
for 30 minutes. Methyl iodide (0.283 ml) was added to the  
mixture and the solution was stirred at 0°C for 1 hour. The  
20 reaction was quenched with water and then the aqueous  
solution was extracted with ethyl acetate. The organic layer  
was washed with brine and dried over sodium sulfate. The  
solvent was evaporated in vacuo to give N-[2-[4,4-dimethyl-  
(2,5-oxazolinyl)]phenyl]-N-methyl-3-methoxy-4-  
25 methoxycarbonylbenzamide (1.5 g).

NMR (CDCl<sub>3</sub>, δ) : 1.35 (3H, s), 1.36 (3H, s), 3.33 (3H,  
s), 3.63 (3H, s), 4.00-4.14 (2H, m), 6.93-7.09 (3H,  
m), 7.18-7.36 (2H, m), 7.57 (1H, d, J=8Hz), 7.78  
(1H, d, J=8Hz)

30

#### Preparation 65

The following compounds were obtained according to a  
similar manner to that of Preparation 64.

- 35 1) N-[2-[4,4-Dimethyl(2,5-oxazolinyl)]phenyl]-N-methyl-3-

## methoxy-4-nitrobenzamide

NMR (CDCl<sub>3</sub>, δ) : 1.38 (3H, s), 1.39 (3H, s), 3.35 (3H, s), 3.71 (3H, s), 4.02-4.16 (2H, m), 7.00-7.10 (2H, m), 7.21 (1H, s), 7.23-7.39 (2H, m), 7.63 (1H, d, J=8Hz), 7.80 (1H, m)

## 2) 3-Methoxy-4-methoxycarbonyl-N-methyl-N-[2-(morpholin-4-yl)phenyl]benzamide

NMR (CDCl<sub>3</sub>, δ) : 2.32-2.48 (2H, m), 2.78-2.91 (2H, m), 3.50 (3H, s), 3.61 (3H, s), 3.62-3.80 (4H, m), 3.82 (3H, s), 6.86 (1H, d, J=8Hz), 6.91 (1H, s), 7.02-7.32 (4H, m), 7.59 (1H, d, J=8Hz)

## 3) 3-Methoxy-N-methyl-N-[2-(morpholin-4-yl)phenyl]-4-nitrobenzamide

NMR (CDCl<sub>3</sub>, δ) : 2.28-2.45 (2H, m), 2.77-2.92 (2H, m), 3.50 (3H, s), 3.57-3.82 (7H, m), 6.87 (1H, d, J=8Hz), 7.02 (1H, s), 7.04-7.18 (2H, m), 7.19-7.33 (2H, m), 7.61 (1H, d, J=8Hz)

## 4) 3-Methoxy-4-methoxycarbonyl-N-methyl-N-[2-(1-pyrrolyl)phenyl]benzamide

NMR (CDCl<sub>3</sub>, δ) : 3.43 (3H, s), 3.66 (3H, s), 3.81 (3H, s), 6.25 (2H, s), 6.38-6.51 (3H, m), 6.56 (1H, s), 7.12 (1H, m), 7.21-7.51 (4H, m)

## 5) 3-Methoxy-4-methoxycarbonyl-N-methyl-N-(2-piperidinophenyl)benzamide

NMR (CDCl<sub>3</sub>, δ) : 1.43-1.72 (6H, m), 2.29-2.44 (2H, m), 2.70-2.84 (2H, m), 3.50 (3H, s), 3.60 (3H, s), 3.81 (3H, s), 6.84 (1H, d, J=8Hz), 6.90 (1H, s), 6.98-7.09 (2H, m), 7.15 (1H, dd, J=8, 8Hz), 7.22 (1H, d, J=8Hz), 7.59 (1H, d, J=8Hz)

## 6) 3-Methoxy-N-methyl-4-nitro-N-(2-piperidinophenyl)-

benzamide

NMR (CDCl<sub>3</sub>,  $\delta$ ) : 1.42-1.76 (6H, m), 2.23-2.41 (2H, m),  
2.70-2.87 (2H, m), 3.53 (3H, s), 3.68 (3H, s), 6.87  
(1H, d, J=8Hz), 7.01 (1H, s), 7.03-7.14 (2H, m),  
5 7.20 (1H, dd, J=8, 8Hz), 7.27 (1H, m), 7.64 (1H, d,  
J=8Hz)

7) N-Methyl-3-methoxy-4-methoxycarbonyl-N-[2-(4-methyl-1-  
piperazinyl)phenyl]benzamide

10 NMR (CDCl<sub>3</sub>,  $\delta$ ) : 2.34 (3H, s), 2.39-2.61 (6H, m), 2.82-  
2.99 (2H, m), 3.49 (3H, s), 3.61 (3H, s), 3.82 (3H,  
s), 6.81-6.93 (2H, m), 7.00-7.11 (2H, m), 7.12-7.29  
(2H, m), 7.60 (1H, d, J=8Hz)

15 8) N-Methyl-3-methoxy-N-[2-(4-methyl-1-piperazinyl)phenyl]-  
4-nitrobenzamide

NMR (CDCl<sub>3</sub>,  $\delta$ ) : 2.34 (3H, s), 2.35-2.62 (6H, m), 2.85-  
3.00 (2H, m), 3.52 (3H, s), 3.68 (3H, s), 6.89 (1H,  
d, J=8Hz), 7.01 (1H, s), 7.04-7.32 (4H, m), 7.64  
20 (1H, d, J=8Hz)

9) 3-Methoxy-4-methoxycarbonyl-N-methyl-N-[2-(2,5-  
oxazolyl)phenyl]benzamide

25 NMR (CDCl<sub>3</sub>,  $\delta$ ) : 3.45 (3H, s), 3.60 (3H, s), 3.80 (3H,  
s), 6.69 (1H, d, J=8Hz), 6.72 (1H, s), 7.22-7.42  
(4H, m), 7.48 (1H, d, J=8Hz), 7.76 (1H, s), 7.89  
(1H, d, J=8Hz)

30 10) N-Methyl-3-methoxy-4-methoxycarbonyl-N-[2-(2,5-  
oxazoliny)phenyl]benzamide

NMR (CDCl<sub>3</sub>,  $\delta$ ) : 3.40 (3H, s), 3.67 (3H, s), 3.81 (3H,  
s), 4.02-4.12 (2H, m), 4.30-4.46 (2H, m), 6.88-6.98  
(2H, m), 7.12 (1H, d, J=8Hz), 7.24 (1H, dd, J=8,  
8Hz), 7.35 (1H, dd, J=8, 8Hz), 7.57 (1H, d, J=8Hz),  
35 7.76 (1H, d, J=8Hz)

- 11) N-Methyl-3-methoxy-4-methoxycarbonyl-N-[2-(3H, 4H, 5H-2, 6-oxazinyl)phenyl]benzamide

NMR (CDCl<sub>3</sub>, δ) : 1.92-2.08 (2H, m), 3.40 (3H, s), 3.58 (2H, t, J=7Hz), 3.64 (3H, s), 3.82 (3H, s), 4.27-4.40 (2H, m), 6.93-7.00 (1H, m), 7.01-7.09 (2H, m), 7.16-7.28 (2H, m), 7.51-7.65 (2H, m)

- 12) N-[2-(1-Aza-3-oxaspiro[4.4]non-1-en-2-yl)phenyl]-3-methoxy-4-methoxycarbonyl-N-methylbenzamide

NMR (CDCl<sub>3</sub>, δ) : 1.59-1.77 (4H, m), 1.80-2.05 (4H, m), 3.36 (3H, s), 3.65 (3H, s), 3.80 (3H, s), 4.15-4.27 (2H, m), 6.93-7.03 (2H, m), 7.06 (1H, d, J=8Hz), 7.18-7.35 (2H, m), 7.58 (1H, d, J=8Hz), 7.75 (1H, m)

#### Preparation 66

To a solution of 2-(1-pyrrolyl)nitrobenzene (1.11 g) in ethanol (30 ml) were added iron powder (1.65 g) and acetic acid (3.54 g) and the mixture was refluxed for 1 hour. The reaction mixture was filtered through a bed of celite and the filtrate was concentrated in vacuo. The residue was diluted with a mixture of ethyl acetate and saturated aqueous sodium bicarbonate solution and the mixture was filtered through a bed of celite again. The organic layer was separated and washed with water and brine. The solution was dried over sodium sulfate and the solvent was evaporated in vacuo to give 2-(1-pyrrolyl)phenylamine (860 mg).

NMR (CDCl<sub>3</sub>, δ) : 3.72 (2H, br s), 6.31-6.40 (2H, m), 6.72-6.90 (4H, m), 7.10-7.24 (2H, m)

#### Preparation 67

The following compounds were obtained according to a similar manner to that of Preparation 66.

- 1) 4-Amino-3-methoxy-N-methyl-N-(2-piperidinophenyl)-



## benzamide

NMR (CDCl<sub>3</sub>, δ) : 1.43-1.71 (6H, m), 2.54-2.68 (2H, m),  
2.71-2.86 (2H, m), 3.46 (3H, s), 3.57 (3H, s), 3.86  
(2H, s), 6.41 (1H, d, J=8Hz), 6.83 (1H, s), 6.86-  
7.00 (3H, m), 7.07-7.19 (2H, m)

2) 4-Amino-N-methyl-3-methoxy-N-[2-(4-methyl-1-piperazinyl)phenyl]benzamide

NMR (CDCl<sub>3</sub>, δ) : 2.35 (3H, s), 2.41-2.61 (4H, m), 2.66-  
2.80 (2H, m), 2.84-3.00 (2H, m), 3.46 (3H, s), 3.58  
(3H, s), 3.88 (2H, s), 6.42 (1H, d, J=8Hz), 6.82  
(1H, s), 6.86-7.06 (3H, m), 7.09-7.21 (2H, m)

3) 2-(2,5-Oxazolinyl)phenylamine

NMR (CDCl<sub>3</sub>, δ) : 4.10 (2H, t, J=8Hz), 4.34 (2H, t,  
J=8Hz), 6.60-6.76 (2H, m), 7.20 (1H, dd, J=8, 8Hz),  
7.71 (1H, d, J=8Hz)

4) 2-(3H,4H,5H-2,6-Oxazinyl)phenylamine

NMR (CDCl<sub>3</sub>, δ) : 1.91-2.02 (2H, m), 3.63 (2H, t,  
J=7Hz), 4.35 (2H, t, J=7Hz), 6.20 (2H, br s), 6.56-  
6.68 (2H, m), 7.12 (1H, dd, J=8, 8Hz), 7.70 (1H, d,  
J=8Hz)

5) 4-Amino-2-(N,N-dimethylcarbamoyl)-1H-benzimidazole

NMR (DMSO-d<sub>6</sub>, δ) : 3.06 (3H x 3/5, s), 3.09 (3H x 2/5,  
s), 3.65 (3H x 3/5, s), 3.19 (3H x 2/5, s), 5.35  
(2H x 3/5, s), 5.48 (2H x 2/5, s), 6.36 (1H x 3/5,  
d, J=8Hz), 6.45 (1H x 2/5, d, J=8Hz), 6.66 (1H x  
3/5, d, J=8Hz), 6.88-7.02 (1H + 1H x 2/5, m), 7.15  
(1H, br peak)

Preparation 68

To a solution of 3-nitro-1,2-phenylenediamine (1.0 g)  
and triethylamine (793 mg) in dichloromethane (3 ml) under

nitrogen was added portionwise phthalylglycyl chloride (1.61 g) in ice water bath and the mixture was stirred at the same temperature for 2 hours. The reaction mixture was washed with saturated sodium bicarbonate aqueous solution, dried  
5 over magnesium sulfate and evaporated in vacuo. To the resulting crude product was added polyphosphoric acid (5 ml) and stirred at 130°C for 3 hours. After the mixture was cooled at ambient temperature, ammonia solution (28%) was added to the reaction mixture in ice water bath. The  
10 precipitate was collected by vacuum filtration to give 2-phthalimidomethyl-4-nitro-1H-benzimidazole (1.35 g).

NMR (DMSO-d<sub>6</sub>, δ) : 5.13 (2H, s), 7.36 (1H, t, J=8Hz),  
7.86-8.05 (5H, m), 8.11 (1H, d, J=8Hz)

15 Preparation 69

The following compound was obtained according to a similar manner to that of Preparation 68.

4-Nitro-2-(2-phthalimidoethyl)-1H-benzimidazole

20 NMR (DMSO-d<sub>6</sub>, δ) : 3.28 (2H, t, J=7.5Hz), 4.05 (2H, t, J=7.5Hz), 7.34 (1H, t, J=8Hz), 7.78-7.90 (4H, m),  
7.96 (1H, d, J=8Hz), 8.08 (1H, d, J=8Hz)

Preparation 70

25 To a solution of 2-chloro-4-nitro-1H-benzimidazole (300 mg) in N-methyl-2-pyrrolidone (4 ml) was added imidazole (517 mg) and the mixture was stirred at 80°C for 8 hours. The reaction mixture was poured into brine and extracted with a mixture of chloroform and methanol. The organic layer was  
30 dried over magnesium sulfate and evaporated in vacuo. The residue was chromatographed on silica gel eluting with a mixture of chloroform and methanol (100-0 - 30-1) to give 2-(1-imidazolyl)-4-nitro-1H-benzimidazole (175 mg).

35 NMR (DMSO-d<sub>6</sub>, δ) : 7.21 (1H, s), 7.46 (1H, t, J=8Hz),  
8.05-8.19 (3H, m), 8.70 (1H, s)

Preparation 71

The following compound was obtained according to a similar manner to that of Preparation 70.

## 5      4-Nitro-2-(1,2,4-tetrazol-1-yl)-1H-benzimidazole

NMR (DMSO-d<sub>6</sub>, δ) : 7.50 (1H, t, J=8Hz), 8.06 (1H, br peak), 8.17 (1H, d, J=8Hz), 8.50 (1H, s), 9.53 (1H, s)

10     Preparation 72

A mixture of 2-chloro-4-nitro-1H-benzimidazole (300 mg) and N,N-dimethylethylenediamine (2 ml) were stirred at 80°C for 8 hours. The reaction mixture was poured into saturated sodium bicarbonate aqueous solution and extracted with a mixture of chloroform and methanol. The organic layer was washed with brine, dried over magnesium sulfate and evaporated in vacuo. The residue was washed with diisopropyl ether to give 2-[[2-(dimethylamino)ethyl]amino]-4-nitro-1H-benzimidazole (113 mg).

20      NMR (CDCl<sub>3</sub>, δ) : 2.65 (3H, s), 2.90-2.98 (2H, m), 3.55-3.64 (2H, m), 7.11 (1H, t, J=8Hz), 7.69 (1H, d, J=8Hz), 7.87 (1H, d, J=8Hz)

Preparation 73

25      The following compounds were obtained according to a similar manner to that of Preparation 72.

## 1) 2-(4-Methylpiperazin-1-yl)-4-nitro-1H-benzimidazole

30      NMR (CDCl<sub>3</sub>, δ) : 2.42 (3H, s), 2.58-2.72 (4H, m), 3.63-3.80 (4H, m), 7.19 (1H, t, J=8Hz), 7.68 (1H, d, J=8Hz), 7.85 (1H, d, J=8Hz), 9.44 (1H, br s)

## 2) 2-Dimethylamino-4-nitro-1H-benzimidazole

35      NMR (CDCl<sub>3</sub>, δ) : 3.30 (6H, s), 7.21 (1H, t, J=8Hz), 7.76 (1H, d, J=8Hz), 7.86 (1H, d, J=8Hz)

- 3) 2-[(2-Aminoethyl)methylamino]-4-nitro-1H-benzimidazole  
NMR (CDCl<sub>3</sub>, δ) : 3.09 (2H, t, J=5Hz), 3.26 (3H, s),  
3.60 (2H, t, J=5Hz), 7.15 (1H, t, J=8Hz), 7.61 (1H,  
d, J=8Hz), 7.83 (1H, d, J=8Hz)

5

- 4) 2-[(2-Methylamino)ethyl]amino-4-nitro-1H-benzimidazole  
NMR (CDCl<sub>3</sub>, δ) : 2.68 (3H, s), 3.09 (2H, t-like,  
J=5Hz), 3.59 (2H, t-like, J=5Hz), 7.02 (1H, t,  
J=8Hz), 7.51 (1H, d, J=8Hz), 7.74 (1H, d, J=8Hz)

10

- 5) 2-[[2-(Dimethylamino)ethyl]methylamino]-4-nitro-1H-  
benzimidazole  
NMR (CDCl<sub>3</sub>, δ) : 2.58 (6H, s), 2.81-2.91 (2H, m), 3.34  
(3H, s), 3.50-3.60 (2H, m), 7.09 (1H, t, J=8Hz),  
7.70 (1H, d, J=8Hz), 7.83 (1H, d, J=8Hz)

15

- 6) 2-[(2-Methoxyethyl)amino]-4-nitro-1H-benzimidazole  
NMR (CDCl<sub>3</sub>, δ) : 3.50 (3H, s), 3.60-3.73 (4H, m), 5.60  
(1H, br peak), 7.15 (1H, t, J=8Hz), 7.63 (1H, d,  
J=8Hz), 7.83 (1H, d, J=8Hz)

20

#### Preparation 74

To a solution of ethyl 2-chloromethyl-1H-benzimidazole-  
4-carboxylate (250 mg) in dichloroethane (2.5 ml) was added  
25 morpholine (183 mg) under ice bath cooling and the reaction  
mixture was stirred at ambient temperature for 15 hours. To  
the reaction mixture was added morpholine (91 mg) and stirred  
at 80°C for 6 hours. After the reaction mixture was  
concentrated in vacuo, the residue was diluted with  
30 chloroform and saturated sodium hydrogen carbonate aqueous  
solution. The organic layer was separated and washed with  
brine. The solution was dried over magnesium sulfate and  
concentrated in vacuo. The residue was purified by silica  
gel column chromatography (methanol:chloroform = 1:9) to give  
35 ethyl 2-morpholinomethyl-1H-benzimidazole-4-carboxylate (219

mg).

NMR (CDCl<sub>3</sub>,  $\delta$ ) : 1.47 (3H, t, J=7Hz), 2.57-2.60 (4H, m), 3.75-3.77 (4H, m), 3.86 (2H, s), 4.47 (2H, q, J=8Hz), 7.28 (1H, t, J=8Hz), 7.90 (1H, d, J=8Hz), 7.91 (1H, d, J=8Hz)

#### Preparation 75

The following compounds were obtained according to a similar manner to that of Preparation 74.

1) 2-(N,N-Dimethylaminomethyl)-4-nitro-1H-benzimidazole

NMR (CDCl<sub>3</sub>,  $\delta$ ) : 2.36 (6H, s), 3.81 (2H, s), 7.35 (1H, t, J=8Hz), 8.03 (1H, d, J=8Hz), 8.15 (1H, d, J=8Hz)

2) 2-(1-Imidazolyl)methyl-4-nitro-1H-benzimidazole

NMR (DMSO-d<sub>6</sub>,  $\delta$ ) : 5.53 (2H, s), 6.91 (1H, s), 7.28 (1H, s), 7.40 (1H, t, J=8Hz), 7.80 (1H, s), 8.08 (1H, d, J=8Hz), 8.14 (1H, d, J=8Hz)

3) 2-[(4-Methylpiperazin-1-yl)methyl]-4-nitro-1H-benzimidazole

NMR (CDCl<sub>3</sub>,  $\delta$ ) : 2.40 (3H, s), 2.49-2.82 (8H, m), 3.91 (2H, s), 7.35 (1H, t, J=8Hz), 8.04 (1H, d, J=8Hz), 8.16 (1H, d, J=8Hz)

4) 2-(Morpholin-4-ylmethyl)-4-nitro-1H-benzimidazole

NMR (CDCl<sub>3</sub>,  $\delta$ ) : 2.55-2.69 (4H, m), 3.73-3.85 (4H, m), 3.89 (2H, s), 7.35 (1H, t, J=8Hz), 8.05 (1H, d, J=8Hz), 8.15 (1H, d, J=8Hz)

5) 4-Nitro-2-(pyrrolidin-1-ylmethyl)-1H-benzimidazole

NMR (CDCl<sub>3</sub>,  $\delta$ ) : 1.96 (4H, br s), 2.86 (4H, br s), 4.19 (2H, s), 7.36 (1H, t, J=8Hz), 8.03 (1H, d, J=8Hz), 8.16 (1H, d, J=8Hz)

## 6) 4-Nitro-2-(piperidinomethyl)-1H-benzimidazole

NMR (CDCl<sub>3</sub>, δ) : 1.58 (2H, br peak), 1.73 (4H, br peak), 2.65 (4H, br peak), 4.00 (2H, br s), 7.36 (1H, t, J=8Hz), 8.03 (1H, d, J=8Hz), 8.17 (1H, d, J=8Hz)

5

## 7) 2-[2-(Dimethylamino)ethyl]-4-nitro-1H-benzimidazole

NMR (CDCl<sub>3</sub>, δ) : 2.50 (6H, s), 2.83 (2H, t, J=7Hz), 3.18 (2H, t, J=8Hz), 7.30 (1H, t, J=8Hz), 8.00 (1H, d, J=8Hz), 8.11 (1H, d, J=8Hz)

10

## 8) 2-[2-(4-Methylpiperazin-1-yl)ethyl]-4-nitro-1H-benzimidazole

NMR (CDCl<sub>3</sub>, δ) : 2.41 (3H, s), 2.70 (8H, br peak), 2.89 (2H, t, J=5Hz), 3.18 (2H, t, J=5Hz), 7.32 (1H, t, J=8Hz), 8.01 (1H, d, J=8Hz), 8.13 (1H, d, J=8Hz)

15

## 9) Ethyl 2-dimethylaminomethyl-1H-benzimidazole-4-carboxylate

NMR (CDCl<sub>3</sub>, δ) : 1.44 (3H, t, J=7Hz), 2.33 (6H, s), 3.77 (2H, s), 4.45 (2H, q, J=7Hz), 7.27 (1H, t, J=8Hz), 7.88-7.92 (2H, m)

20

## 10) Ethyl 2-(4-methylpiperazin-1-yl)methyl-1H-benzimidazole-4-carboxylate

NMR (CDCl<sub>3</sub>, δ) : 1.47 (3H, t, J=7Hz), 2.51 (4H, br s), 2.62 (4H, br s), 3.86 (2H, s), 4.47 (2H, q, J=8Hz), 7.26 (1H, t, J=8Hz), 7.90 (2H, d, J=8Hz)

25

## 11) Ethyl 2-(4-dimethylaminopiperidino)methyl-1H-benzimidazole-4-carboxylate

NMR (CDCl<sub>3</sub>, δ) : 1.46 (3H, t, J=7Hz), 1.61 (2H, dt, J=2, 8Hz), 1.82 (1H, br s), 2.12-2.23 (4H, m), 2.28 (6H, s), 2.92-2.98 (2H, m), 3.82 (2H, s), 4.48 (2H, q, J=7Hz), 7.28 (1H, t, J=8Hz), 7.89 (2H, d, J=8Hz)

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Preparation 76

A suspension of 2-methyl-4-nitrobenzimidazole (2.2 g) in 1,4-dioxane (35 ml) was treated with triethylamine (2.51 g) and di-tert-butyl dicarbonate (5.42 g). After 15 minutes, to the reaction mixture was added N,N-dimethylaminopyridine (catalytic amount). The solution was stirred a further 20 hours and concentrated in vacuo and the residue was dissolved in ethyl acetate. The solution was washed with 1N hydrochloric acid, water, saturated aqueous sodium hydrogen carbonate and brine. The organic layer was dried over magnesium sulfate. The solvent was evaporated in vacuo and the residue was purified by silica gel column chromatography (chloroform) to give tert-butyl 2-methyl-4-nitro-1H-benzimidazole-1-carboxylate (3.0 g).

NMR (CDCl<sub>3</sub>,  $\delta$ ) : 1.73 (9H, s), 2.93 (3H, s), 7.41 (1H, dd, J=8, 8Hz), 8.13 (1H, d, J=8Hz), 8.29 (1H, d, J=8Hz)

Preparation 77

The following compounds were obtained according to a similar manner to that of Preparation 76.

1) Ethyl 2-(N-tert-butoxycarbonylaminomethyl)-1-methyl-1H-benzimidazole-4-carboxylate

NMR (CDCl<sub>3</sub>,  $\delta$ ) : 1.40-1.50 (12H, m), 3.34 (3H, s), 4.49 (2H, q, J=7.5Hz), 4.70 (2H, d, J=7Hz), 5.48 (1H, br peak), 7.33 (1H, t, J=8Hz), 7.53 (1H, d, J=8Hz), 7.94 (1H, d, J=8Hz)

2) Ethyl 2-(N-tert-butoxycarbonylaminomethyl)-3-methyl-3H-benzimidazole-4-carboxylate

NMR (CDCl<sub>3</sub>,  $\delta$ ) : 1.44 (3H, t, J=7.5Hz), 1.48 (9H, s), 3.93 (3H, s), 4.44 (2H, q, J=7.5Hz), 4.64 (2H, d, J=5Hz), 5.51 (1H, br peak), 7.25 (1H, t, J=8Hz), 7.77 (1H, d, J=8Hz), 7.88 (1H, d, J=8Hz)

162

3) 2-[(tert-Butoxy)carbonylamino]-4-nitro-1H-benzimidazole

NMR (DMSO-d<sub>6</sub>, δ) : 1.68 (9H, s), 7.11 (1H, t, J=8Hz),  
7.84-8.00 (3H, m)

5     Preparation 78

To a solution of N-(2-chloroethyl)-2-nitrobenzamide  
(3.63 g) in acetonitrile (100 ml) was slowly added 40%  
potassium fluoride on alumina (10 g). This slurry was  
stirred at ambient temperature for 24 hours. The potassium  
10 fluoride on alumina was filtered through a bed of celite,  
washed with ethyl acetate. The solvent was evaporated to  
give 2-(2,5-oxazolinylnitrobenzene (3.0 g).

NMR (CDCl<sub>3</sub>, δ) : 4.09 (2H, t, J=8Hz), 4.45 (2H, t,  
J=8Hz), 7.58-7.69 (2H, m), 7.80-7.89 (2H, m)

15

Preparation 79

The following compound was obtained according to a  
similar manner to that of Preparation 78.

20     2-(2-Nitrophenyl)-4H,5H,6H-1,3-oxazine

NMR (CDCl<sub>3</sub>, δ) : 1.96-2.11 (2H, m), 3.56-3.68 (2H,  
m), 4.25-4.37 (2H, m), 7.54 (1H, dd, J=8, 8Hz),  
7.61 (1H, dd, J=8, 8Hz), 7.71 (1H, d, J=8Hz), 7.85  
(1H, d, J=8Hz)

25

Preparation 80

The following compound was obtained according to a  
similar manner to that of Example 84.

30     Benzyl 2-formylindole-4-carboxylate

NMR (DMSO-d<sub>6</sub>, δ) : 5.45 (2H, s), 7.30-7.55 (6H, m),  
7.73-7.82 (2H, m), 7.88 (1H, d, J=8Hz), 9.93 (1H,  
s)

35     Preparation 81



The following compound was obtained according to a similar manner to that of Example 107.

4-Methyl-1-(2-nitrophenyl)piperazine

5 NMR (CDCl<sub>3</sub>, δ) : 2.36 (3H, s), 2.52-2.61 (4H, m), 3.03-3.12 (4H, m), 7.03 (1H, dd, J=8, 8Hz), 7.15 (1H, d, J=8Hz), 7.48 (1H, dd, J=8, 8Hz), 7.75 (1H, d, J=8Hz)

10 Preparation 82

To a solution of indole-4-carboxylic acid (500 mg) in methanol (9 ml) and conc. hydrochloric acid (1.0 ml) was added a portion of sodium cyanoborohydride (487 mg) at 0°C and the mixture was stirred at ambient temperature for 1  
15 hour. The suspension was diluted with water (10 ml) and then the clear solution was neutralized with 2N sodium hydroxide aqueous solution. Methanol was removed and the aqueous solution was diluted with dioxane (15 ml) and 1N sodium hydroxide aqueous solution (10 ml). To the mixture was added  
20 portionwise di-tert-butyl dicarbonate (813 mg) and the solution was stirred at ambient temperature for 2 hours. The solution was neutralized with 1N hydrochloric acid and diluted with ethyl acetate (30 ml). The resulting solution was washed with brine, dried over magnesium sulfate and  
25 concentrated in vacuo. The solid was triturated with diethyl ether:n-hexane (1:9) to give 1-tert-butoxycarbonylindoline-4-carboxylic acid (727 mg).

30 NMR (DMSO-d<sub>6</sub>, δ) : 1.50 (9H, s), 3.36 (2H, t, J=9Hz), 3.92 (2H, t, J=9Hz), 7.27 (1H, t, J=8Hz), 7.49 (1H, d, J=8Hz), 7.80-7.94 (1H, br)

Preparation 83

To a solution of methyl trans-2-[β-(dimethylamino)vinyl]-3-nitrobenzoate (3.16 g) in  
35 tetrahydrofuran (20 ml) and pyridine (3.57 ml) was added

dropwise benzyloxyacetyl chloride (4.2 g) at ambient temperature and the mixture was refluxed for 3 hours. The resulting mixture was diluted with ethyl acetate and the solution was washed successively with water, saturated sodium bicarbonate aqueous solution and brine. Drying, filtering and removal of solvents afforded a crude product. The crude product was purified by column chromatography to give 2-[ $\beta$ -(dimethylamino)- $\alpha$ -(benzyloxyacetyl)vinyl]-3-nitrobenzoate (3.32 g).

10 NMR (CDCl<sub>3</sub>,  $\delta$ ) : 2.70-2.80 (6H, br s), 3.80 (3H, s), 4.08-4.16 (2H, br s), 4.50 and 4.51 (Total 2H, s), 7.28-7.38 (5H, m), 7.49 (1H, t, J=8Hz), 7.79 (1H, d, J=8Hz), 7.80 (1H, s), 7.89 (1H, d, J=8Hz)

15 Preparation 84

A solution of 2-[ $\beta$ -(dimethylamino)- $\alpha$ -(benzyloxyacetyl)vinyl]-3-nitrobenzoate (3.31 g) and p-toluenesulfonic acid hydrate (632 mg) in 1,4-dioxane (15 ml) and water (5 ml) was refluxed for 24 hours. The resulting mixture was evaporated in vacuo and the residue was diluted with ethyl acetate. The organic layer was washed successively with water and brine. Drying, filtering and removal of solvents afforded a crude product as a dark-red oil. The crude product was purified by silica gel column chromatography (eluent; hexane:ethyl acetate = 3:1) to give 3-benzyloxymethyl-5-nitroisocoumarin (1.0 g).

25 NMR (CDCl<sub>3</sub>,  $\delta$ ) : 4.40 (2H, s), 4.69 (2H, s), 7.29-7.42 (5H, m), 7.43 (1H, s), 7.62 (1H, t, J=8Hz), 8.47 (1H, d, J=8Hz), 8.60 (1H, d, J=8Hz),

30

Preparation 85

A solution of 3-benzyloxymethyl-5-nitroisocoumarin (850 mg) in methanol (40.0 ml) was treated with aqueous titanium trichloride (11.2 ml), added as a single portion. After stirring 2 hours at ambient temperature, water (100 ml) and chloroform (120 ml) were added. The whole was carefully basified with saturated sodium bicarbonate aqueous solution and the organic layer was separated. The aqueous layer was further extracted with chloroform (120 ml) and the combined extract was washed with water, dried over magnesium sulfate, and concentrated to afford 3-benzyloxymethyl-5-aminoisocoumarin (806 mg).

NMR (CDCl<sub>3</sub>,  $\delta$ ) : 3.89-4.00 (2H, br), 4.38 (2H, s), 4.69 (2H, s), 6.50 (1H, s), 7.01 (1H, d, J=9Hz), 7.29 (1H, t, J=9Hz), 7.30-7.40 (5H, m), 7.73 (1H, d, J=9Hz)

#### Preparation 86

A mixture of 5-amino-3-benzyloxymethylisocoumarin (800 mg) and sodium methylate in methanol (768 mg) was stirred at ambient temperature for 20 minutes. After removal of solvents, water (40 ml) was added to the residue and the whole was extracted with chloroform. The extract was washed with water, dried over magnesium sulfate, and evaporated to dryness to leave a crude product, which was purified by silica gel column chromatography with n-hexane:ethyl acetate (6:1) as an eluent to afford methyl 2-benzyloxymethylindole-4-carboxylate (660 mg).

NMR (CDCl<sub>3</sub>,  $\delta$ ) : 3.98 (3H, s), 4.57 (2H, s), 4.78 (2H, s), 7.08 (1H, s), 7.22 (1H, t, J=8Hz), 7.29-7.39 (5H, m), 7.54 (1H, d, J=8Hz), 7.90 (1H, d, J=8Hz), 8.50-8.56 (1H, br)

#### Preparation 87

To a solution of methyl 2-benzyloxymethylindole-4-carboxylate (650 mg) in methanol (27 ml) and concentrated

hydrochloric acid (3.0 ml) was added sodium cyanoborohydride (968 mg) with ice-bath stirring and the mixture was stirred at ambient temperature for 2.5 hours. The resulting mixture was diluted with water (30 ml) and basified with saturated sodium bicarbonate aqueous solution. The mixture was extracted with ethyl acetate (40 ml) and the organic layer was washed successively with water and brine, dried over magnesium sulfate and concentrated in vacuo. The residue was purified by silica gel column chromatography (eluent; n-hexane:ethyl acetate = 6:1) to give methyl 2-benzyloxymethylindoline-4-carboxylate (550 mg).

NMR (CDCl<sub>3</sub>,  $\delta$ ) : 3.02 (1H, dd, J=8, 17Hz), 3.41-3.58 (3H, m), 3.88 (3H, s), 4.08-4.18 (1H, m), 4.33-4.41 (1H, br), 4.55 (2H, s), 6.74 (1H, d, J=8Hz), 7.08 (1H, t, J=8Hz), 7.28-7.39 (6H, m)

#### Preparation 88

The Vilsmeier reagent was prepared by the dropwise addition of phosphoryl oxychloride (0.75 mg) to cooled N,N-dimethylformamide (20.0 ml) under constant stirring. A solution of methyl indole-4-carboxylate in N,N-dimethylformamide (12.0 ml) was added to the above solution at 0°C and the solution was stirred for 30 minutes. The mixture was diluted with water (40 ml) and the solution was neutralized with saturated sodium bicarbonate aqueous solution and extracted with ethyl acetate (60 ml). The organic layer was washed successively with water and brine, dried over magnesium sulfate and concentrated in vacuo. The solid was triturated with diethyl ether (7 ml) to give methyl 3-formylindole-4-carboxylate (792 mg).

NMR (CDCl<sub>3</sub>,  $\delta$ ) : 4.00 (3H, s), 7.32 (1H, t, J=9Hz), 7.64 (1H, d, J=9Hz), 7.83 (1H, d, J=9Hz), 8.06 (1H, d, J=3Hz), 9.78-9.88 (1H, br), 10.53 (1H, s)

#### Preparation 89

To a solution of 2,2,6,6-tetramethylpiperidine (1.97 g) in tetrahydrofuran (24.0 ml) was added dropwise n-butyllithium (6.8 ml, 1.64M solution in n-hexane) at -40°C and the mixture was stirred at 0°C for 30 minutes. A solution of methyl 1-methoxymethoxyindole-4-carboxylate (1.64 g) in tetrahydrofuran (12.0 ml) was added to the above solution at -60°C and the solution was stirred at the same temperature for 30 minutes. A solution of N,N-dimethylformamide (662 mg) in tetrahydrofuran (9.0 ml) was added to the reaction mixture at -60°C and the solution was stirred at the same temperature for 2 hours. The temperature was raised to -30°C and the reaction was quenched with saturated ammonium chloride aqueous solution. The aqueous solution was extracted with ethyl acetate (80 ml) and the organic layer was washed with brine. Drying, filtering and removal of solvents afforded a crude product. The crude product was purified by silica gel column chromatography (eluent; n-hexane:ethyl acetate = 9:1) to give methyl 2-formyl-1-methoxymethoxyindole-4-carboxylate (1.15 g).

NMR (CDCl<sub>3</sub>, δ) : 3.67 (3H, s), 4.01 (3H, s), 5.34 (2H, s), 7.50 (1H, t, J=9Hz), 7.77 (1H, d, J=9Hz), 7.81 (1H, s), 7.98 (1H, d, J=9Hz), 9.98 (1H, s)

#### Preparation 90

To a solution of benzyl 1-tert-butoxycarbonyl-2-hydroxymethylindole-4-carboxylate (465 mg), phthalimide (179 mg) and triphenylphosphine (640 mg) in tetrahydrofuran (15.0 ml) was added diethyl azodicarboxylate (425 mg) and the mixture was stirred at ambient temperature for 1 hour. The resulting mixture was concentrated in vacuo and the residue was chromatographed on silica gel with n-hexane:ethyl acetate (6:1). The solid was triturated with methanol to give benzyl 1-tert-butoxycarbonyl-2-phthalimidomethylindole-4-carboxylate (440 mg).

NMR (CDCl<sub>3</sub>, δ) : 1.72 (9H, s), 5.27 (2H, s), 5.29 (2H,

168

s), 6.95 (1H, s), 7.21-7.34 (6H, m), 7.75-7.81 (2H, m), 7.89-7.94 (2H, m), 7.96 (1H, d, J=8Hz), 8.37 (1H, d, J=8Hz)

5     Preparation 91

      The mixture of tert-butyl 2-methyl-4-nitro-1H-benzimidazole-1-carboxylate (3.0 g) and 10% palladium on carbon (300 mg) in methanol (25 ml) and 1,4-dioxane (60 ml) was hydrogenated under atmospheric pressure at ambient  
10    temperature for 11 hours. The reaction mixture was filtered through a bed of celite and the filtrate was concentrated in vacuo to give crude product. The solid was washed with diisopropyl ether/n-hexane (1/2) to give 4-amino-2-methyl-1H-benzimidazole-1-carboxylate (2.0 g).

15       NMR (CDCl<sub>3</sub>, δ) : 1.70 (9H, s), 2.79 (3H, s), 4.28 (2H, br), 6.58 (1H, d, J=8Hz), 7.06 (1H, dd, J=8, 8Hz), 7.25 (1H, d, J=8Hz)

Preparation 92

20       A solution of N-[(1-hydroxymethyl)cyclopentyl]-2-nitrobenzamide (2.1 g) in thionyl chloride (5.8 ml) was stirred at ambient temperature for 1 hour. To the reaction mixture was added diethyl ether and the resulting precipitate was filtered. The collected precipitate was dissolved in  
25    ethyl acetate and 1N sodium hydroxide. The organic layer was washed with brine and dried over magnesium sulfate and concentrated to give 4-aza-3-(2-nitrophenyl)-2-oxaspiro[4.4]-non-3-ene (1.95 g).

      NMR (CDCl<sub>3</sub>, δ) : 1.62-1.79 (4H, m), 1.82-2.10 (4H, m),  
30       4.26 (2H, s), 7.54-7.67 (2H, m), 7.80 (1H, d, J=8Hz), 7.88 (1H, d, J=8Hz)

Preparation 93

      To a suspension of methyl 2-formyl-1H-benzimidazole-4-  
35    carboxylate (460 mg) in a mixture of water (3.2 ml) and

t-butyl alcohol (12 ml) were added 2-methyl-2-butene (700 mg) and sodium dihydrogenphosphate (387 mg) in water bath. To the mixture was added portionwise sodium chlorite (901 mg) and stirred for 1 day at same temperature. The reaction mixture was cooled in an ice bath, adjusted to pH 4 with 1N hydrochloric acid and the precipitate was collected by vacuum filtration. The precipitate was washed with ethyl acetate and methanol to give methyl 2-carboxy-1H-benzimidazole-4-carboxylate (400 mg).

10        MASS (ES-) (m/z) : 219

#### Preparation 94

To a solution of 3-ethoxycarbonyl-1,2-phenylenediamine (790 mg) in tetrahydrofuran (10 ml) was added 1,1'-thiocarbonyldiimidazole (1.02 g) in ice water bath and the mixture was stirred for 20 hours at ambient temperature. The reaction solvent was concentrated in vacuo and the residue was washed with chloroform and collected by vacuum filtration to give ethyl 2-mercapto-1H-benzimidazole-4-carboxylate (665 mg).

NMR (DMSO-d<sub>6</sub>, δ) : 1.33 (3H, t, J=7.5Hz), 4.42 (2H, q, J=7.5Hz), 7.23 (1H, t, J=8Hz), 7.38 (1H, d, J=8Hz), 7.66 (1H, d, J=8Hz)

#### 25    Preparation 95

To a solution of ethyl 2-mercapto-1H-benzimidazole-4-carboxylate (500 mg) were added iodomethane (351 mg) and potassium carbonate (622 mg) at ambient temperature and the mixture was stirred for 20 hours at same temperature. The reaction mixture was poured into water and extracted with chloroform. The organic layer was washed with water and brine, dried over magnesium sulfate and evaporated in vacuo. The residue was washed with diisopropyl ether to give ethyl 2-methylthio-1H-benzimidazole-4-carboxylate (310 mg).

35        NMR (CDCl<sub>3</sub>, δ) : 1.44 (3H, t, J=7.5Hz), 3.80 (3H, s),

170

4.44 (2H, q, J=7.5Hz), 7.24 (1H, t, J=8Hz), 7.77-  
7.88 (2H, m)

#### Preparation 96

5 To a solution of ethyl 2-methylthio-1H-benzimidazole-4-  
carboxylate (200 mg) in dichloromethane (4 ml) was added  
dropwise a solution of m-chloroperoxybenzoic acid (292 mg)  
in dichloromethane (4 ml) in ice water bath under nitrogen  
and the mixture was stirred for 4 hours at the same  
10 temperature. The reaction mixture was poured into water and  
extracted with dichloromethane. The organic layer was washed  
with water, dried over magnesium sulfate and evaporated in  
vacuo. The residue was purified by preparative thin-layer  
chromatography (chloroform:ethyl acetate:methanol = 16:1:1) to  
15 give ethyl 2-methylsulfonyl-1H-benzimidazole-4-carboxylate  
(102 mg).

NMR (CDCl<sub>3</sub>,  $\delta$ ) : 1.48 (3H, t, J=7.5Hz), 3.42 (3H, s),  
4.50 (2H, q, J=7.5Hz), 7.49 (1H, t, J=8Hz), 8.06-  
8.16 (2H, m)

20

#### Preparation 97

To a suspension of ethyl 2-mercapto-1H-benzimidazole-4-  
carboxylate (950 mg) in 20% acetic acid aqueous solution (30  
ml) at 0°C was bubbled chlorine for 30 minutes. The  
25 resulting crude product was collected by vacuum filtration  
and added portionwise to ammonia aqueous solution (28%, 10  
ml) in ice water bath. The reaction mixture was stirred at  
ambient temperature for 1 hour and adjusted to pH 5 with 1N  
hydrochloric acid. The precipitate was collected by vacuum  
30 filtration to give ethyl 2-sulfamoyl-1H-benzimidazole-4-  
carboxylate (775 mg).

NMR (DMSO-d<sub>6</sub>,  $\delta$ ) : 1.38 (3H, t, J=7.5Hz), 4.43 (2H, q,  
J=7.5Hz), 7.47 (1H, t, J=8Hz), 7.97 (1H, d, J=8Hz),  
8.04 (1H, d, J=8Hz)

35



Preparation 98

Thionyl chloride (8.3 ml) was added dropwise to 2-hydroxymethyl-4-nitro-1H-benzimidazole (1.15 g) at 0°C and the suspension was then heated at reflux for 3 hours. The excess of thionyl chloride was removed in vacuo, and the residue was poured into ice and adjusted to pH 7 with saturated sodium bicarbonate aqueous solution. The precipitate was collected by vacuum filtration and washed water to give 2-chloromethyl-4-nitro-1H-benzimidazole (1.32 g).

NMR (DMSO-d<sub>6</sub>, δ) : 4.98 (2H, s), 7.39 (1H, t, J=8Hz), 8.09 (1H, d, J=8Hz), 8.13 (1H, d, J=8Hz)

Preparation 99

To a solution of 2,4-dihydroxy-8-methylquinazoline (1.00 g) in mixture of 2-methyl-2-propanol (20 ml) and water (20 ml) was added potassium permanganate (3.59 g) and magnesium sulfate (1.37 g) and the reaction mixture was stirred at 90°C for 15 hours. After the reaction mixture was filtered through a bed of celite, the filtrate was diluted with water. The solution was adjusted to pH 4 with 1N hydrochloric acid. The formed precipitate was collected by vacuum filtration to give 2,4-dihydroxyquinazoline-8-carboxylic acid (390 mg).

NMR (DMSO-d<sub>6</sub>, δ) : 7.31 (1H, t, J=8Hz), 8.19 (1H, d, J=8Hz), 8.18 (1H, d, J=8Hz)

Preparation 100

To a solution of ethyl 3-aminopyrazole-4-carboxylate (5.00 g) in carbon tetrachloride (70 ml) was added triethyl orthoacetate (6.53 g) and the reaction mixture was stirred at 90°C for 3 hours. After the reaction mixture was concentrated in vacuo, the residue was purified by silica gel (Chromatorex, Fuji Silysia Chemical Ltd.) column chromatography (n-hexane:ethyl acetate = 1:2) to give ethyl 3-(1-aza-2-ethoxyprop-1-enyl)pyrazole-4-carboxylate (4.94 g)

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NMR (CDCl<sub>3</sub>, δ) : 1.27-1.36 (6H, m), 1.92 (3H, s), 4.22-4.36 (4H, m), 7.91 (1H, s)

#### Preparation 101

5 To a solution of ethyl 3-(1-aza-2-ethoxyprop-1-enyl)pyrazole-4-carboxylate (4.90 g) in N,N-dimethylformamide (50 ml) was added hydroxylamine hydrochloride (15.1 g) and stirred at ambient temperature for 3 hours. The reaction mixture was concentrated in vacuo and the residue was diluted  
10 with water. The solution was adjusted to pH 7 with 1N hydrochloric acid. The formed precipitate was collected by vacuum filtration to give ethyl 3-[[1-(hydroxyimino)ethyl]-amino]pyrazole-4-carboxylate (1.52 g).

15 NMR (DMSO-d<sub>6</sub>, δ) : 1.27 (3H, t, J=8Hz), 2.20 (3H, s), 4.22 (2H, q, J=8Hz), 8.16 (1H, s), 8.07 (1H, s), 9.82 (1H, s)

#### Preparation 102

To a solution of ethyl 3-[[1-(hydroxyimino)ethyl]amino]-  
20 pyrazole-4-carboxylate (1.50 g) and pyridine (1.12 g) in N,N-dimethylformamide (20 ml) was added dropwise p-toluenesulfonyl chloride (1.39 g) under ice bath cooling and stirred at ambient temperature for 3 hours. The reaction mixture was diluted with ethyl acetate and water. The  
25 organic layer was separated and washed with saturated sodium hydrogen carbonate aqueous solution and brine. The solution was dried over magnesium sulfate and concentrated in vacuo to give ethyl 3-[1-(p-toluenesulfonyloxyimino)ethyl]amino-1H-pyrazole-4-carboxylate (2.14 g).

30 NMR (CDCl<sub>3</sub>, δ) : 1.42 (3H, t, J=8Hz), 2.30 (3H, s), 2.43 (3H, s), 4.38 (2H, q, J=8Hz), 7.33 (2H, d, J=8Hz), 7.90-7.93 (3H, m), 9.10 (1H, s)

#### Preparation 103

35 A solution of ethyl 3-[1-(p-toluenesulfonyloxyimino)-

ethyl]amino-1H-pyrazole-4-carboxylate (1.00 g) and pyridine (240 mg) in ethanol (20 ml) was refluxed for 3 hours. The reaction mixture was concentrated in vacuo and the residue was diluted with water. The solution was adjusted to pH 4 with 1N hydrochloric acid. The formed precipitate was collected by vacuum filtration to give ethyl 2-methyl-1H-pyrazolo[1,5-b][1,2,4]triazole-7-carboxylate (240 mg).

NMR (DMSO-d<sub>6</sub>, δ) : 1.29 (3H, t, J=8Hz), 2.45 (3H, s), 4.23 (2H, q, J=8Hz), 7.85 (1H, s)

#### Preparation 104

To a solution of ethyl 3-aminophthalic acid (1.00 g) in ethanol (10 ml) was added formamidine hydrochloride (444 mg) and refluxed for 12 hours. After cooling, the formed precipitate was collected by vacuum filtration and the precipitate was washed with ethanol to give 4-hydroxyquinazoline-5-carboxylic acid (504 mg).

NMR (DMSO-d<sub>6</sub>, δ) : 7.52-7.62 (2H, m), 7.72 (1H, t, J=8Hz), 8.13 (1H, s)

#### Preparation 105

To a solution of ethyl 3-nitro-2-aminobenzoate (700 mg) in N,N-dimethylaniline (7 ml) was added dropwise isonicotinoyl chloride (2.96 g) at 120°C for 3 hours. After cooling, the reaction mixture was diluted with ethyl acetate and saturated sodium hydrogen carbonate aqueous solution. The organic layer was separated and washed with brine. The solution was dried over magnesium sulfate and concentrated in vacuo. The residue was purified by silica gel column chromatography (n-hexane:ethyl acetate = 9:1) to give ethyl 3-nitro-2-(4-pyridyl)carbonylaminobenzoate (200 mg).

NMR (CDCl<sub>3</sub>, δ) : 1.42 (3H, t, J=7Hz), 4.43 (2H, q, J=7Hz), 7.26 (1H, s), 7.40 (1H, t, J=7Hz), 7.82-7.84 (2H, m), 8.15 (1H, d, J=8Hz), 8.31 (1H, d, J=8Hz), 8.85 (1H, d, J=7Hz)

Preparation 106

To a solution of ethyl 3-nitro-2-(4-pyridyl)-  
carbonylaminobenzoate (200 mg) in ethanol (2 ml) was added  
iron (177 mg) and acetic acid (381 mg) at ambient temperature  
5 and the reaction mixture was stirred at 60°C for 2 hours.  
After the reaction mixture was filtered through a bed of  
celite, the filtrate was concentrated in vacuo. The residue  
was diluted with chloroform and saturated sodium hydrogen  
carbonate aqueous solution. The organic layer was separated  
10 and washed with brine. The solution was dried over magnesium  
sulfate and concentrated in vacuo to give ethyl 2-(4-  
pyridyl)-1H-benzimidazole-4-carboxylate (150 mg).

NMR (CDCl<sub>3</sub>, δ) : 1.48 (3H, t, J=7Hz), 4.40 (2H, q,  
J=7Hz), 7.38 (1H, t, J=8Hz), 7.90-8.00 (3H, m),  
15 8.05 (1H, d, J=8Hz), 8.82 (1H, d, J=6Hz)

Preparation 107

To a solution of ethyl 3-amino-2-hydroxybenzoate (500  
mg), sodium hydrogen carbonate (927 mg) and  
20 benzyltributylammonium bromide (983 mg) in chloroform (10 ml)  
was added dropwise chloroacetyl chloride (374 mg) in  
chloroform (3 ml) under ice bath cooling. The reaction  
mixture was stirred at ambient temperature for 1 hour and at  
60°C for 2 hours. To the reaction mixture was added dropwise  
25 chloroacetyl chloride (312 mg) in chloroform (3 ml) under ice  
bath cooling and stirred at 60°C for 2 hours. After the  
reaction mixture was concentrated in vacuo, the residue was  
diluted with chloroform and saturated sodium hydrogen  
carbonate aqueous solution. The organic layer was separated  
30 and washed with brine. The solution was dried over magnesium  
sulfate and concentrated in vacuo to give ethyl 2H-1,4-  
benzoxazin-3-one-8-carboxylate (460 mg).

NMR (CDCl<sub>3</sub>, δ) : 1.38 (3H, t, J=7Hz), 4.36 (2H, q,  
J=8Hz), 4.71 (2H, s), 6.96-7.00 (2H, m), 7.47-7.52  
35 (1H, m), 9.04 (1H, s)

Example 40

The following compounds were obtained according to a similar manner to that of Example 1.

- 5      1) 4-(Imidazo[1,5-a]pyridine-1-carbonyl)amino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide
- 10                      NMR (CDCl<sub>3</sub>, δ) : 1.48-1.58 (2H, m), 1.65-1.88 (4H, m), 2.27 (3H, s), 2.29 (3H, s), 2.32-2.40 (6H, m), 3.33 (3H, s), 3.46-3.51 (2H, m), 3.59-3.67 (2H, m), 3.80 (3H, s), 3.81-3.99 (2H, m), 6.58 (1H, d, J=8Hz), 6.62 (1H, s), 6.74-6.87 (2H, m), 6.93 (1H, d, J=8Hz), 7.00 (1H, s), 7.02-7.09 (1H, m), 8.01 (1H, d, J=8Hz), 8.03 (1H, s), 8.29 (1H, d, J=9Hz), 8.36 (1H, d, J=8Hz), 9.60 (1H, s)
- 15
- 20      2) 4-[(1-tert-Butoxycarbonyl-2-ethoxycarbonylindolin-4-yl)carbonyl]amino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]-benzamide
- 25                      NMR (CDCl<sub>3</sub>, δ) : 1.28 (3H, t, J=8Hz), 1.52 (9H, s), 1.55-1.88 (6H, m), 2.28 (3H, s), 2.31 (3H, s), 2.32-2.43 (6H, m), 3.32 (3H, s), 3.42-3.53 (3H, m), 3.60-3.67 (2H, m), 3.78 (3H, s), 3.80-4.00 (3H, m), 4.19 (2H, q, J=8Hz), 4.82-4.91 (1H, m), 6.59 (1H, d, J=8Hz), 6.62 (1H, s), 6.84 (1H, d, J=8Hz), 6.92 (1H, d, J=8Hz), 7.02 (1H, s), 7.20 (1H, d, J=8Hz), 7.26-7.32 (1H, m), 8.02-8.10 (1H, m), 8.20 (1H, d, J=8Hz), 8.42 (1H, s)
- 30
- 35      3) 4-[(1-tert-Butoxycarbonylindolin-4-yl)carbonyl]amino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide
- NMR (CDCl<sub>3</sub>, δ) : 1.48-1.60 (2H, m), 1.56 (9H, s), 1.66-1.88 (4H, m), 2.28 (3H, s), 2.30 (3H, s),

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2.31-2.42 (6H, m), 3.31 (3H, s), 3.40 (2H, t, J=9Hz), 3.47-3.51 (2H, m), 3.59-3.67 (2H, m), 3.78 (3H, s), 3.84-4.04 (4H, m), 6.58 (1H, d, J=8Hz), 6.62 (1H, s), 6.84 (1H, d, J=8Hz), 6.92 (1H, d, J=8Hz), 7.02 (1H, s), 7.20 (1H, t, J=8Hz), 7.23-7.29 (1H, m), 8.01 (1H, s), 8.23 (1H, d, J=8Hz), 8.38 (1H, s)

- 4) 4-[(2-Benzyloxymethyl-1-tert-butoxycarbonylindolin-4-yl)carbonyl]amino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]-benzamide

NMR (CDCl<sub>3</sub>, δ) : 1.50 (9H, s), 1.51-1.58 (2H, m), 1.66-1.87 (4H, m), 2.28 (3H, s), 2.30 (3H, s), 2.32-2.41 (6H, m), 3.32 (3H, s), 3.41-3.53 (5H, m), 3.59-3.67 (3H, m), 3.76 (3H, s), 3.83-3.99 (2H, m), 4.48 (2H, s), 4.57-4.65 (1H, br), 6.58 (1H, d, J=8Hz), 6.63 (1H, s), 6.84 (1H, d, J=8Hz), 6.92 (1H, d, J=8Hz), 7.02 (1H, s), 7.19-7.30 (8H, m), 8.26 (1H, d, J=8Hz), 8.38 (1H, s)

- 5) 4-[(1-tert-Butoxycarbonyl-3-tert-butylidiphenylsilyloxy-methylindol-4-yl)carbonyl]amino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide

NMR (CDCl<sub>3</sub>, δ) : 0.90 (9H, s), 1.50-1.60 (2H, m), 1.67 (9H, s), 1.68-1.89 (4H, m), 2.22 (3H, s), 2.30 (3H, s), 2.32-2.42 (6H, m), 3.33 (3H, s), 3.46-3.51 (2H, m), 3.60-3.67 (5H, m), 3.87-3.98 (2H, m), 4.88 (2H, s), 6.53 (1H, d, J=8Hz), 6.62 (1H, s), 6.83 (1H, d, J=8Hz), 6.93 (1H, d, J=8Hz), 6.98 (1H, s), 7.21-7.41 (8H, m), 7.50-7.59 (5H, m), 8.16 (1H, s), 8.26 (1H, d, J=8Hz), 8.34 (1H, d, J=8Hz)

- 6) 4-[(1-tert-Butoxycarbonyl-2-tert-butylidiphenylsilyloxy-

methylinol-4-yl)carbonyl]amino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide

5 NMR (CDCl<sub>3</sub>, δ) : 0.90 (9H, s), 1.50-1.60 (2H, m), 1.67  
(9H, s), 1.68-1.89 (4H, m), 2.22 (3H, s), 2.30 (3H,  
s), 2.32-2.42 (6H, m), 3.33 (3H, s), 3.46-3.51 (2H,  
m), 3.60-3.67 (5H, m), 3.87-3.98 (2H, m), 4.88 (2H,  
s), 6.53 (1H, d, J=8Hz), 6.62 (1H, s), 6.83 (1H, d,  
J=8Hz), 6.93 (1H, d, J=8Hz), 6.98 (1H, s), 7.21-  
10 7.41 (8H, m), 7.50-7.59 (5H, m), 8.16 (1H, s), 8.26  
(1H, d, J=8Hz), 8.34 (1H, d, J=8Hz)

7) 4-[(1-tert-Butoxycarbonyl-2-phthalimidomethylinol-4-yl)carbonyl]amino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]-benzamide

15 NMR (CDCl<sub>3</sub>, δ) : 1.46-1.57 (2H, m), 1.64-1.85 (4H, m),  
1.73 (9H, s), 2.25 (3H, s), 2.30 (3H, s), 2.32-2.41  
(6H, m), 3.30 (3H, s), 3.44-3.51 (2H, m), 3.60-3.67  
20 (2H, m), 3.72 (3H, s), 3.81-3.96 (2H, m), 5.29 (2H,  
s), 6.54 (1H, d, J=8Hz), 6.59 (1H, s), 6.78 (1H,  
s), 6.83 (1H, d, J=8Hz), 6.98 (1H, s), 7.32 (1H, t,  
J=8Hz), 7.54 (1H, d, J=8Hz), 7.77-7.81 (2H, m),  
7.88-7.93 (2H, m), 8.03 (1H, s), 8.18 (1H, d,  
25 J=8Hz), 8.31 (1H, d, J=8Hz), 8.42 (1H, s)

8) 4-[(1-tert-Butoxycarbonyl-2-methylinol-4-yl)carbonyl]-amino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide

30 NMR (CDCl<sub>3</sub>, δ) : 1.48-1.60 (2H, m), 1.65-1.90 (4H, m),  
1.69 (9H, s), 2.28 (3H, s), 2.29 (3H, s), 2.32-2.43  
(6H, m), 2.62 (3H, s), 3.33 (3H, s), 3.47-3.53 (2H,  
m), 3.60-3.68 (2H, m), 3.78 (3H, s), 3.86-4.00 (2H,  
m), 6.59 (1H, d, J=8Hz), 6.63 (1H, s), 6.83-6.98  
35 (3H, m), 7.05 (1H, s), 7.24-7.31 (1H, m), 7.57 (1H,

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d, J=8Hz), 8.28-8.37 (2H, m), 8.53 (1H, s)

- 9) 4-[(1-tert-Butoxycarbonylindolin-6-yl)carbonyl]amino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide

NMR (CDCl<sub>3</sub>, δ) : 1.50-1.63 (2H, m), 1.58 (9H, s), 1.67-1.88 (4H, m), 2.28 (3H, s), 2.30 (3H, s), 2.32-2.42 (6H, m), 3.12 (2H, t, J=8Hz), 3.32 (3H, s), 3.46-3.51 (2H, m), 3.60-3.67 (2H, m), 3.77 (3H, s), 3.85-3.99 (2H, m), 4.03 (2H, t, J=8Hz), 6.58 (1H, d, J=8Hz), 6.63 (1H, s), 6.84 (1H, d, J=8Hz), 6.90 (1H, d, J=8Hz), 7.00 (1H, s), 7.21 (1H, d, J=8Hz), 7.45 (1H, d, J=8Hz), 8.24 (1H, d, J=8Hz), 8.47 (1H, s)

- 10) 4-[(1-tert-Butoxycarbonylindol-6-yl)carbonyl]amino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide

NMR (CDCl<sub>3</sub>, δ) : 1.48-1.59 (2H, m), 1.67-1.90 (4H, m), 1.70 (9H, s), 2.28 (3H, s), 2.30 (3H, s), 2.32-2.42 (6H, m), 3.33 (3H, s), 3.47-3.52 (2H, m), 3.60-3.67 (2H, m), 3.79 (3H, s), 3.83-4.00 (2H, m), 6.58 (1H, d, J=8Hz), 6.61 (1H, d, J=3Hz), 6.63 (1H, s), 6.86 (1H, d, J=8Hz), 6.93 (1H, d, J=8Hz), 7.03 (1H, s), 7.62 (1H, d, J=9Hz), 7.72 (1H, d, J=9Hz), 7.75 (1H, d, J=3Hz), 8.30 (1H, d, J=8Hz), 8.60 (1H, s), 8.67 (1H, s)

- 11) 3-Methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]-4-(quinolin-8-yl)-carbonylaminobenzamide

NMR (CDCl<sub>3</sub>, δ) : 1.48-1.59 (2H, m), 1.65-1.76 (2H, m), 1.78-1.89 (2H, m), 2.24 (3H, s), 2.26 (3H, s), 2.31-2.41 (6H, m), 3.32 (3H, s), 3.43-3.50 (2H, m), 3.58-3.66 (2H, m), 3.83-3.99 (2H, m), 3.88 (3H, s),



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6.54-6.64 (2H, m), 6.87 (1H, d, J=8Hz), 6.97 (1H, d, J=8Hz), 7.03 (1H, s), 7.50 (1H, dd, J=8, 7Hz), 7.70 (1H, t, J=8Hz), 7.87 (1H, d, J=8Hz), 8.31 (1H, d, J=8Hz), 8.50 (1H, d, J=8Hz), 8.88 (1H, d, J=7Hz), 8.98 (1H, m)

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- 12) 4-(3-Hydroxy-1H-indazol-4-yl)carbonylamino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide

10 NMR (CDCl<sub>3</sub>, δ) : 1.47-1.58 (2H, m), 1.66-1.78 (2H, m), 1.78-1.89 (2H, m), 2.27 (3H, s), 2.37 (3H, s), 2.43-2.54 (6H, m), 3.33 (3H, s), 3.52-3.57 (2H, m), 3.64-3.72 (2H, m), 3.79 (3H, s), 3.85-4.00 (2H, m), 6.54-6.65 (2H, m), 6.80-7.02 (3H, m), 7.34-7.49  
15 (2H, m), 7.58 (1H, d, J=8Hz), 8.26 (1H, d, J=8Hz), 9.32 (1H, br)

- 13) 3-Methoxy-N-methyl-N-(4-methyl-2-benzyloxyphenyl)-4-[2-(tert-butoxycarbonyl)aminomethyl-1H-benzimidazol-4-yl]carbonylaminobenzamide

20 NMR (CDCl<sub>3</sub>, δ) : 1.48 (9H, s), 2.23 (3H, s), 3.39 (3H, s), 3.61 (3H, s), 4.52 (2H, d, J=7Hz), 4.87 (1H, d, J=12Hz), 5.03 (1H, d, J=12Hz), 5.60 (1H, br), 6.60-6.70 (2H, m), 6.85-7.00 (3H, m), 7.21-7.40 (6H, m),  
25 7.48 (1H, d, J=8Hz), 8.10 (1H, d, J=8Hz), 8.47 (1H, d, J=8Hz)

- 14) N-(2,4-Dimethylphenyl)-3-methoxy-N-methyl-4-[2-(tert-butoxycarbonylaminomethyl)-1H-benzimidazol-4-yl]carbonylaminobenzamide

30 NMR (CDCl<sub>3</sub>, δ) : 1.50 (9H, s), 2.14 (3H, s), 2.25 (3H, s), 3.37 (3H, s), 3.74 (3H, s), 4.57 (2H, d, J=7Hz), 5.64 (1H, br), 6.86-6.99 (7H, m), 7.31 (1H, t, J=8Hz), 7.51 (1H, br), 8.10 (1H, br), 8.47 (1H, br)  
35

- 15) 3-Methoxy-N-(2-methoxy-4-methylphenyl)-N-methyl-4-[2-(tert-butoxycarbonylaminomethyl)-1H-benzimidazol-4-yl]-carbonylamino benzamide

5 NMR (CDCl<sub>3</sub>, δ) : 1.49 (9H, s), 2.28 (3H, s), 3.34 (3H, s), 3.71 (3H, s), 3.77 (3H, s), 4.57 (2H, d, J=7Hz), 5.69 (1H, br), 6.56-6.63 (2H, m), 6.86-6.98 (3H, m), 7.29 (1H, t, J=8Hz), 7.50 (1H, d, J=8Hz), 8.09 (1H, d, J=8Hz), 8.50 (1H, d, J=8Hz)

- 10 16) 3-Methoxy-N-methyl-N-[4-methyl-2-[4-(4-methylpiperazin-1-yl)carbonylphenylmethoxy]phenyl]-4-[2-(tert-butoxycarbonyl)aminomethyl-1H-benzimidazol-4-yl]carbonylamino benzamide

15 MASS (m/z) : 776

- 17) 3-Methoxy-N-methyl-N-[4-methyl-2-[3-(4-methylpiperazin-1-yl)carbonylprop-1-yloxy]phenyl]-4-[2-(tert-butoxycarbonylaminomethyl)-1H-benzimidazol-4-yl]carbonylamino benzamide

20 NMR (CDCl<sub>3</sub>, δ) : 1.50 (9H, s), 2.06-2.17 (2H, m), 2.26 (3H, s), 2.31-2.39 (4H, m), 2.50 (2H, t, J=7.5Hz), 3.33 (3H, s), 3.43-3.50 (2H, m), 3.52-3.70 (2H, m), 3.81 (3H, s), 3.85-4.06 (2H, m), 4.58 (2H, m), 6.60-6.68 (2H, m), 6.89-7.05 (3H, m), 7.33 (1H, t, J=8Hz), 7.51 (1H, d, J=8Hz), 8.12 (1H, d, J=8Hz), 8.51 (1H, d, J=8Hz)

- 18) 3-Methoxy-N-methyl-N-[4-methyl-2-[4-(4-methylpiperazin-1-yl)carbonylbut-1-yloxy]phenyl]-4-[2-(tert-butoxycarbonyl)aminomethyl-1H-benzimidazol-4-yl]carbonylamino benzamide

30 NMR (CDCl<sub>3</sub>, δ) : 1.51 (9H, s), 1.64-1.73 (2H, m), 1.76-1.88 (2H, m), 2.26 (6H, s), 2.28 (3H, s), 2.32-2.47 (6H, m), 3.33 (3H, s), 3.43-3.51 (2H, m), 3.58-3.68 (2H, m), 3.76-4.00 (5H, m), 4.60 (2H, m), 5.83 (1H,

br ), 6.41 (1H, d, J=8Hz), 6.54-6.64 (2H, m), 6.78-7.03 (3H, m), 7.42 (1H, d, J=8Hz), 8.10 (1H, d, J=8Hz), 8.50 (1H, d, J=8Hz)

- 5 19) N-[2-(4-Ethoxycarbonylpent-1-yloxy)-4-methylphenyl]-3-methoxy-N-methyl-4-(3-nitro-2-phthalimidomethylcarbonylaminophenyl)carbonylaminobenzamide

10 NMR (CDCl<sub>3</sub>, δ) : 1.24 (3H, t, J=7.5Hz), 1.44-1.58 (2H, m), 1.64-1.77 (2H, m), 1.77-1.90 (2H, m), 2.28 (3H, s), 2.33 (2H, t, J=7.5Hz), 3.34 (3H, s), 3.72 (3H, s), 3.82-4.00 (2H, m), 4.11 (2H, q, J=7.5Hz), 4.49 (2H, s), 6.60-6.68 (2H, m), 6.88 (1H, d, J=8Hz), 6.98 (1H, s), 7.38 (1H, t, J=8Hz), 7.72-7.90 (6H, m), 8.02 (1H, d, J=8Hz), 8.40 (1H, s)

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- 20) 4-[2-Carbamoyl-1-(4-methoxybenzyl)-1H-benzimidazol-4-yl]carbonylamino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]-benzamide

20 NMR (CDCl<sub>3</sub>, δ) : 1.47-1.63 (2H, m), 1.63-1.77 (2H, m), 1.77-1.91 (2H, m), 2.24 (3H, s), 2.29 (3H, s), 2.31-2.42 (6H, m), 3.33 (3H, s), 3.43-3.53 (2H, m), 3.58-3.68 (2H, m), 3.75 (3H, s), 3.80-3.90 (4H, m), 3.90-4.00 (1H, m), 5.98 (2H, s), 6.02 (1H, br s), 25 6.55-6.65 (2H, m), 6.81 (2H, d, J=8Hz), 6.88 (1H, d, J=8Hz), 6.98 (1H, d, J=8Hz), 7.10 (1H, s), 7.21 (2H, d, J=8Hz), 7.48 (1H, t, J=8Hz), 7.62 (1H, d, J=8Hz), 7.84 (1H, s), 8.24 (1H, d, J=8Hz), 8.51 (1H, d, J=8Hz)

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- 21) 4-[2-(N,N-Dimethylcarbamoyl)-1-(4-methoxybenzyl)-1H-benzimidazol-4-yl]carbonylamino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide

35 NMR (CDCl<sub>3</sub>, δ) : 1.49-1.64 (2H, m), 1.64-1.78 (2H, m),

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- 1.78-1.90 (2H, m), 2.27 (3H, s), 2.30 (3H, s),  
 2.33-2.44 (6H, m), 3.13 (3H, s), 3.19 (3H, s), 3.34  
 (3H, s), 3.46-3.54 (2H, m), 3.60-3.69 (2H, m),  
 3.74-3.81 (6H, m), 3.81-4.01 (2H, m), 5.55 (2H, s),  
 5 6.58 (1H, d, J=8Hz), 6.64 (1H, s), 6.80-6.90 (3H,  
 m), 6.84 (1H, d, J=8Hz), 7.06 (1H, s), 7.16 (2H, d,  
 J=8Hz), 7.44 (1H, t, J=8Hz), 7.56 (1H, d, J=8Hz),  
 8.24 (1H, d, J=8Hz), 8.47 (1H, d, J=8Hz)
- 10 22) 4-[2-[1-(Benzyloxycarbonyl)-4-piperidyl]-1H-  
 benzimidazol-4-yl]carbonylamino-3-methoxy-N-methyl-N-[4-  
 methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-  
 yloxy]phenyl]benzamide  
 NMR (DMSO-d<sub>6</sub>, δ) : 1.37-1.49 (2H, m), 1.49-1.61 (2H,  
 15 m), 1.67-1.79 (2H, m), 1.79-1.92 (2H, m), 2.07-2.35  
 (14H, m), 3.07 (2H, br peak), 3.15-3.29 (4H, m),  
 3.29-3.46 (4H, m), 3.68 (3H, s), 3.84 (1H, br  
 peak), 3.94 (1H, br peak), 4.11-4.22 (2H, m), 5.11  
 (2H, s), 6.63 (1H, d, J=8Hz), 6.81 (1H, s), 6.88-  
 20 6.97 (2H, m), 7.04 (1H, d, J=8Hz), 7.26-7.45 (6H,  
 m), 7.70 (1H, d, J=8Hz), 7.90 (1H, d, J=8Hz), 8.43  
 (1H, d, J=8Hz)
- 23) 4-[2-(N-tert-Butoxycarbonylaminomethyl)-1-methyl-1H-  
 25 benzimidazol-4-yl]carbonylamino-3-methoxy-N-methyl-N-[4-  
 methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-  
 yloxy]phenyl]benzamide  
 NMR (CDCl<sub>3</sub>, δ) : 1.44-1.56 (11H, m), 1.64-1.75 (2H, m),  
 1.74-1.88 (2H, m), 2.26 (6H, s), 2.30-2.40 (6H, m),  
 30 3.33 (3H, s), 3.43-3.50 (2H, m), 3.58-3.66 (2H, m),  
 3.81 (3H, s), 3.83-4.00 (5H, m), 4.68 (1H, d,  
 J=5Hz), 5.90 (1H, br peak), 6.54-6.64 (2H, m), 6.88  
 (1H, d, J=8Hz), 6.95 (1H, d, J=8Hz), 7.09 (1H, s),  
 7.41 (1H, t, J=8Hz), 7.51 (1H, d, J=8Hz), 8.18 (1H,  
 35 d, J=8Hz), 8.53 (1H, d, J=8Hz)

- 24) 4-[2-(N-tert-Butoxycarbonylaminomethyl)-3-methyl-3H-benzimidazol-4-yl]carbonylamino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide

5 NMR (CDCl<sub>3</sub>, δ) : 1.40-1.61 (2H, m), 1.61-1.91 (4H, m),  
2.22-2.32 (6H, m), 2.32-2.44 (6H, m), 3.33 (3H, s),  
3.43-3.55 (2H, m), 3.58-3.69 (2H, m), 3.74 (3H, s),  
3.82 (3H, s), 3.87-4.03 (2H, m), 4.62 (2H, d,  
J=5Hz), 5.55 (1H, br peak), 6.60 (1H, d, J=8Hz),  
10 6.66 (1H, s), 6.80-6.90 (1H, m), 6.96 (1H, d,  
J=8Hz), 7.04 (1H, s), 7.23-7.32 (1H, m), 7.43 (1H,  
d, J=8Hz), 7.84 (1H, d, J=8Hz), 8.28 (1H, d,  
J=8Hz), 8.34 (1H, s)

- 15 25) 4-(2-Methylthio-1H-benzimidazol-4-yl)carbonylamino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide

NMR (DMSO<sub>6</sub>, δ) : 1.35-1.49 (2H, m), 1.49-1.62 (2H, m),  
1.67-1.80 (2H, m), 2.12 (3H, s), 2.15-2.34 (9H, m),  
20 2.85 (3H, s), 3.19 (3H, s), 3.37-3.46 (4H, m), 3.73  
(3H, s), 3.89 (1H, br peak), 3.96 (1H, br peak),  
6.65 (1H, d, J=8Hz), 6.82 (1H, s), 6.89-6.99 (2H,  
m), 7.03 (1H, d, J=8Hz), 7.28 (1H, t, J=8Hz), 7.61  
(1H, d, J=8Hz), 7.87 (1H, d, J=8Hz), 8.39 (1H, d,  
25 J=8Hz)

- 26) 3-Methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]-4-(2-methylsulfonyl-1H-benzimidazol-4-yl)carbonylaminobenzamide

30 NMR (CDCl<sub>3</sub>, δ) : 1.46-1.63 (2H, m), 1.63-1.78 (2H, m),  
1.78-1.90 (2H, m), 2.24 (3H, s), 2.29 (3H, s),  
2.33-2.44 (6H, m), 3.33 (3H, s), 3.41 (3H, s),  
3.44-3.53 (2H, m), 3.60-3.69 (2H, m), 3.76-3.90  
(4H, m), 3.90-4.02 (1H, m), 6.53-6.64 (2H, m), 6.88  
35 (1H, d, J=8Hz), 6.92-7.02 (2H, m), 7.49 (1H, t,

J=8Hz), 7.77 (1H, d, J=8Hz), 8.09 (1H, d, J=8Hz),  
8.39 (1H, d, J=8Hz)

- 5 27) 3-Methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]-4-(2-sulfamoyl-1H-benzimidazol-4-yl)carbonylaminobenzamide

10 NMR (DMSO-d<sub>6</sub>, δ) : 1.36-1.50 (2H, m), 1.50-1.64 (2H, m), 1.68-1.81 (2H, m), 2.19 (3H, s), 2.23 (3H, s), 2.34-2.38 (6H, m), 3.19 (3H, s), 3.39-3.50 (4H, m), 3.76 (3H, s), 3.87 (1H, br peak), 3.96 (1H, br peak), 6.64 (1H, d, J=8Hz), 6.83 (1H, s), 6.89 (1H, s), 6.95 (1H, d, J=8Hz), 7.03 (1H, d, J=8Hz), 7.50 (1H, t, J=8Hz), 7.82 (1H, d, J=8Hz), 7.98-8.10 (3H, m), 8.36 (1H, d, J=8Hz)

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- 28) 4-(2,4-Dihydroxyquinazolin-8-yl)carbonylamino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide

20 NMR (DMSO-d<sub>6</sub>, δ) : 1.38-1.52 (2H, m), 1.52-1.63 (2H, m), 1.70-1.80 (2H, m), 2.22 (3H, s), 2.23 (3H, s), 2.32-2.43 (6H, m), 3.18 (3H, s), 3.40-3.46 (4H, m), 3.63 (3H, s), 3.80-4.00 (2H, m), 6.65 (1H, d, J=8Hz), 6.82 (1H, s), 6.90-6.93 (2H, m), 7.05 (1H, d, J=8Hz), 7.30 (1H, t, J=8Hz), 7.53 (1H, d, J=8Hz), 8.12 (1H, d, J=8Hz), 8.23 (1H, d, J=8Hz)

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- 29) 3-Methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]-4-(2-methyl-1H-pyrazolo[1,5-b][1,2,4]triazol-7-yl)carbonylamino-benzamide

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35 NMR (DMSO-d<sub>6</sub>, δ) : 1.40-1.50 (2H, m), 1.50-1.62 (2H, m), 1.70-1.80 (2H, m), 2.23 (6H, s), 2.29-2.37 (6H, m), 2.39 (3H, s), 3.19 (3H, s), 3.43-3.47 (4H, m), 3.64 (3H, s), 3.43-3.47 (4H, m), 3.64 (3H, s), 3.80-4.00 (4H, m), 6.63 (1H, d, J=8Hz), 6.78-6.90

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(3H, m), 7.01 (1H, d, J=8Hz), 7.73 (1H, d, J=8Hz),  
8.05 (1H, s), 8.88 (1H, s)

- 30) 4-(4-Hydroxyquinazolin-5-yl)carbonylamino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide  
5 NMR (CDCl<sub>3</sub>, δ) : 1.40-1.55 (2H, m), 1.65-1.80 (4H, m), 2.27 (3H, s), 2.30 (3H, s), 2.33-2.43 (6H, m), 3.33 (3H, s), 3.50 (2H, t, J=7Hz), 3.60-3.67 (5H, m), 3.77-3.97 (2H, m), 6.60-6.65 (2H, m), 6.90-6.95 (2H, m), 7.02 (1H, s), 7.50-7.53 (1H, m), 7.77-7.80 (1H, m), 7.92 (1H, s), 7.98 (1H, s), 8.33 (1H, d, J=8Hz)
- 15 31) 4-(2-Dimethylaminomethyl-1H-benzimidazol-4-yl)carbonylamino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide  
20 NMR (CDCl<sub>3</sub>, δ) : 1.50-1.60 (2H, m), 1.60-1.78 (2H, m), 1.78-1.90 (2H, m), 2.25 (3H, s), 2.27 (3H, s), 2.33-2.40 (12H, m), 3.33 (3H, s), 3.48 (2H, t, J=7Hz), 3.62 (2H, t, J=7Hz), 3.75-4.00 (7H, m), 6.55-6.62 (2H, m), 6.85 (1H, d, J=8Hz), 6.94 (1H, d, J=8Hz), 7.01 (1H, s), 7.33 (1H, t, J=8Hz), 7.57 (1H, d, J=8Hz), 8.15 (1H, d, J=8Hz), 8.50 (1H, d, J=8Hz)  
25
- 32) 3-Methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]-4-[2-(4-methylpiperazin-1-yl)methyl-1H-benzimidazol-4-yl]carbonylaminobenzamide  
30 NMR (CDCl<sub>3</sub>, δ) : 1.50-1.60 (2H, m), 1.67-1.78 (2H, m), 1.78-1.86 (2H, m), 2.26-2.38 (12H, m), 2.48 (4H, br s), 2.62 (4H, br s), 3.32 (3H, s), 3.47 (2H, t, J=7Hz), 3.62 (2H, t, J=7Hz), 3.80-4.00 (7H, m), 6.54-6.63 (2H, m), 6.86 (1H, d, J=8Hz), 6.93-7.03  
35

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(2H, m), 7.28-7.37 (1H, m), 7.58 (1H, d, J=8Hz),  
8.15 (1H, d, J=8Hz), 8.52 (1H, d, J=8Hz)

- 33) 4-[2-(4-Dimethylaminopiperidino)methyl-1H-benzimidazol-  
5 4-yl]carbonylamino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]-benzamide

10 NMR (CDCl<sub>3</sub>, δ) : 1.50-1.93 (8H, m), 2.13-2.40 (17H, m),  
2.92-3.00 (2H, m), 3.32 (3H, s), 3.48 (2H, t,  
J=7Hz), 3.62 (2H, t, J=7Hz), 3.82-4.00 (7H, m),  
6.54-6.62 (2H, m), 6.86 (1H, d, J=8Hz), 6.93-7.05  
(2H, m), 7.35 (1H, t, J=8Hz), 7.59 (1H, d, J=8Hz),  
8.15 (1H, d, J=8Hz), 8.50 (1H, d, J=8Hz)

- 15 34) 3-Methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]-4-(2-morpholinomethyl-1H-benzimidazol-4-yl)carbonylamino benzamide

20 NMR (CDCl<sub>3</sub>, δ) : 1.50-1.60 (2H, m), 1.66-1.77 (2H, m),  
1.78-1.90 (2H, m), 2.25 (3H, s), 2.28 (3H, s),  
2.35-2.40 (6H, m), 2.53-2.62 (4H, m), 3.33 (3H, s),  
3.50 (2H, t, J=7Hz), 3.63 (2H, t, J=7Hz), 3.73-3.77  
(4H, m), 3.81-4.01 (7H, m), 6.56-6.63 (2H, m), 6.87  
(1H, d, J=8Hz), 6.96-7.07 (2H, m), 7.28-7.38 (1H,  
m), 7.50-7.60 (1H, m), 8.17 (1H, d, J=8Hz), 8.52  
25 (1H, d, J=8Hz)

#### Example 41

The following compound was obtained according to a  
similar manner to that of Example 4.

30

- 1) N-[2-[4,4-Dimethyl(2,5-oxazolinyl)]phenyl]-3-methoxy-N-methyl-4-(3-nitro-2-trifluoroacetylaminobenzoyl)-aminobenzamide

35 NMR (CDCl<sub>3</sub>, δ) : 1.36 (3H, s), 1.37 (3H, s), 3.39 (3H, s), 3.63 (3H, s), 4.10 (2H, s), 6.71-7.60 (6H, m),



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7.77 (1H, d, J=8Hz), 7.95 (1H, d, J=8Hz), 8.09 (1H, d, J=8Hz), 8.18 (1H, d, J=8Hz)

5 2) 3-Methoxy-N-methyl-N-[2-(morpholin-4-yl)phenyl]-4-(3-nitro-2-trifluoroacetylaminobenzoyl)aminobenzamide  
NMR (CDCl<sub>3</sub>, δ) : 2.18-2.63 (2H, m), 2.74-2.93 (2H, m), 3.48 (3H, s), 3.54-3.82 (7H, m), 6.87-7.40 (7H, m), 7.91-8.24 (3H, m)

10 3) 3-Methoxy-N-methyl-N-[2-(4-methyl-1-piperazinyl)phenyl]-4-(3-nitro-2-trifluoroacetylaminobenzoyl)aminobenzamide  
NMR (CDCl<sub>3</sub>, δ) : 2.30-3.00 (11H, m), 3.46 (3H, s), 3.59 (3H, s), 6.85-6.96 (2H, m), 7.04 (1H, d, J=8Hz), 7.11-7.24 (2H, m), 7.25-7.39 (2H, m), 7.94 (1H, d, J=8Hz), 8.15 (1H, d, J=8Hz), 8.24 (1H, d, J=8Hz)

15

4) 3-Methoxy-N-methyl-4-(3-nitro-2-trifluoroacetylaminobenzoyl)amino-N-(2-piperidinophenyl)benzamide  
NMR (CDCl<sub>3</sub>, δ) : 1.42-1.74 (6H, m), 2.36-2.65 (2H, m), 2.70-2.88 (2H, m), 3.42-3.76 (6H, m), 6.39-8.24 (10H, m)

20

#### Example 42

25 The following compounds were obtained according to a similar manner to that of Example 7.

1) N-(2-Acetoxy-4-methylphenyl)-4-(2,3-diaminophenyl)-carbonylamino-3-methoxy-N-methylbenzamide  
NMR (CDCl<sub>3</sub>, δ) : 2.30 (6H, sx2), 3.35 (3H, s), 3.70 (3H, s), 6.67 (1H, t, J=8Hz), 6.81-7.05 (6H, m), 8.29 (1H, d, J=8Hz), 8.45 (1H, s)

30

2) 4-(2,3-Diaminophenyl)carbonylamino-3-methoxy-N-(2-methoxycarbonyl-4-methylphenyl)-N-methylbenzamide  
NMR (CDCl<sub>3</sub>, δ) : 2.31 (3H, s), 3.40 (3H, s), 3.71 (3H,

35

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s), 3.85 (3H, s), 6.62 (1H, t, J=8Hz), 6.80 (1H, d, J=8Hz), 6.88 (1H, d, J=8Hz), 6.93 (1H, s), 7.02 (1H, d, J=8Hz), 7.10 (1H, d, J=8Hz), 7.59 (1H, s), 8.19 (1H, d, J=8Hz), 8.42 (1H, s)

5

- 3) 4-(2,3-Diaminophenyl)carbonylamino-3-methoxy-N-methyl-N-[2-(4-phthalimidobut-1-yloxy)-4-methylphenyl]benzamide

Example 43

10 The following compounds were obtained according to a similar manner to that of Example 13.

- 1) N-(2-Acetoxy-4-methylphenyl)-4-(1H-benzimidazol-4-yl)carbonylamino-3-methoxy-N-methylbenzamide

15 NMR (CDCl<sub>3</sub>, δ) : 2.27 (3H, s), 2.30 (3H, s), 3.35 (3H, s), 3.74 (3H, s), 6.86 (1H, s), 6.90-7.03 (3H, m), 7.11 (1H, d, J=8Hz), 7.39 (1H, t, J=8Hz), 7.76 (1H, d, J=8Hz), 7.95 (1H, d, J=8Hz), 8.18 (1H, s), 8.49 (1H, d, J=8Hz)

20

- 2) 4-(1H-Benzimidazol-4-yl)carbonylamino-3-methoxy-N-(2-methoxycarbonyl-4-methylphenyl)-N-methylbenzamide

25 NMR (CDCl<sub>3</sub>, δ) : 2.30 (3H, s), 3.41 (3H, s), 3.70 (3H, s), 3.82 (3H, s), 6.82-6.90 (2H, m), 7.13 (1H, d, J=8Hz), 7.24 (1H, d, J=8Hz), 7.33 (1H, t, J=8Hz), 7.57 (1H, s), 7.72 (1H, d, J=8Hz), 7.98 (1H, d, J=8Hz), 8.10 (1H, s), 8.41 (1H, d, J=8Hz)

Example 44

30 The following compounds were obtained according to a similar manner to that of Example 16.

- 1) 3-Methoxy-N-methyl-4-(2-methyl-1H-benzimidazol-4-yl)carbonylamino-N-[2-(4-phthalimidobut-1-yloxy)-4-methylphenyl]benzamide

35

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5 NMR (CDCl<sub>3</sub>, δ) : 1.77-1.92 (4H, m), 2.22 (3H, s), 2.64 (3H, s), 3.31 (3H, s), 3.69-3.80 (5H, m), 3.89 (1H, m), 3.97 (1H, m), 6.53-6.61 (3H, m), 6.85 (1H, d, J=8Hz), 6.90-6.97 (2H, m), 7.25 (1H, t, J=8Hz), 7.59-7.70 (3H, m), 7.78-7.90 (3H, m), 8.40 (1H, d, J=8Hz)

10 2) 3-Methoxy-N-(2-methoxycarbonyl-4-methylphenyl)-N-methyl-4-(2-methyl-1H-benzimidazol-4-yl)carbonylaminobenzamide  
NMR (CDCl<sub>3</sub>, δ) : 2.30 (3H, s), 2.60 (3H, s), 3.41 (3H, s), 3.70 (3H, s), 3.83 (3H, s), 6.81-6.89 (2H, m), 7.13 (1H, d, J=8Hz), 7.22-7.30 (2H, m), 7.51-7.58 (2H, m), 7.90 (1H, d, J=8Hz), 8.41 (1H, d, J=8Hz)

15 Example 45

The following compounds were obtained according to a similar manner to that of Example 18.

20 1) 3-Methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]-4-[2-(3-phthalimido-propyl)-1H-benzimidazol-4-yl]carbonylaminobenzamide  
NMR (CDCl<sub>3</sub>, δ) : 1.47-1.60 (2H, m), 1.68-1.77 (2H, m), 1.78-1.90 (2H, m), 2.26 (3H, s), 2.28 (3H, s), 2.30-2.40 (8H, m), 3.00 (2H, t, J=7Hz), 3.32 (3H, s), 3.48 (2H, t, J=7Hz), 3.63 (2H, t, J=7Hz), 3.80-4.00 (7H, m), 6.55-6.62 (2H, m), 6.87 (1H, d, J=8Hz), 6.96 (1H, d, J=8Hz), 7.02 (1H, s), 7.32 (1H, t, J=8Hz), 7.60 (1H, d, J=8Hz), 7.66-7.87 (5H, m), 8.10 (1H, d, J=8Hz), 8.49 (1H, d, J=8Hz)

30

2) 3-Methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]-4-(2-phenyl-1H-benzimidazol-4-yl)carbonylaminobenzamide  
NMR (DMSO-d<sub>6</sub>, δ) : 1.40-1.50 (2H, m), 1.50-1.63 (2H, m), 1.70-1.90 (2H, m), 2.13 (3H, s), 2.17-2.23 (4H,

35

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5 m), 2.22 (3H, s), 2.31 (2H, t, J=7Hz), 3.20 (3H, s), 3.39 (4H, br s), 3.87 (3H, s), 3.85-4.00 (2H, m), 6.65 (1H, d, J=8Hz), 6.83 (1H, s), 6.94 (1H, d, J=8Hz), 7.00 (1H, s), 7.04 (1H, d, J=8Hz), 7.40 (1H, t, J=8Hz), 7.57-7.69 (3H, m), 7.80 (1H, d, J=8Hz), 7.97 (1H, d, J=8Hz), 8.32-8.37 (3H, m), 8.50 (1H, d, J=8Hz)

Example 46

10 The following compounds were obtained according to a similar manner to that of Example 23.

- 1) 4-[(2-Ethoxycarbonylindolin-4-yl)carbonyl]amino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide

15 NMR (CDCl<sub>3</sub>, δ) : 1.27 (3H, t, J=8Hz), 1.48-1.59 (2H, m), 1.67-1.89 (4H, m), 2.29 (3H, s), 2.31 (3H, s), 2.36-2.45 (6H, m), 3.32 (3H, s), 3.48-3.53 (2H, m), 3.61-3.72 (3H, m), 3.77 (3H, s), 3.84-4.00 (2H, m), 20 4.09-4.23 (3H, m), 4.41 (1H, dd, J=7, 9Hz), 4.55-4.60 (1H, br s), 6.59 (1H, d, J=8Hz), 6.62 (1H, s), 6.80-6.88 (2H, m), 6.92 (1H, d, J=8Hz), 6.99-7.05 (2H, m), 7.15 (1H, t, J=8Hz), 8.23 (1H, d, J=8Hz), 8.40 (1H, s)

- 25 2) 4-[(Indolin-4-yl)carbonyl]amino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide

30 NMR (CDCl<sub>3</sub>, δ) : 1.49-1.59 (2H, m), 1.67-1.88 (4H, m), 2.28 (3H, s), 2.30 (3H, s), 2.32-2.42 (6H, m), 3.32 (3H, s), 3.36 (2H, t, J=9Hz), 3.47-3.52 (2H, m), 3.56-3.66 (4H, m), 3.78 (3H, s), 3.84-3.99 (2H, m), 6.59 (1H, d, J=8Hz), 6.63 (1H, s), 6.73 (1H, d, J=8Hz), 6.86 (1H, d, J=8Hz), 6.90 (1H, d, J=8Hz), 35 6.97-7.03 (2H, m), 7.09 (1H, t, J=8Hz), 8.27 (1H,

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d, J=8Hz), 8.39 (1H, s)

- 3) 4-[(2-Hydroxymethylindolin-4-yl)carbonyl]amino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide

5  
10  
15  
NMR (CDCl<sub>3</sub>, δ) : 1.47-1.57 (2H, m), 1.65-1.86 (4H, m),  
2.28 (3H, s), 2.32 (3H, s), 2.34-2.45 (6H, m),  
3.06-3.17 (1H, m), 3.32 (3H, s), 3.41-3.52 (3H, m),  
3.57 (1H, dd, J=8, 13Hz), 3.60-3.67 (2H, m), 3.70  
(1H, dd, J=5, 13Hz), 3.77 (3H, s), 3.83-3.98 (2H,  
m), 4.02-4.10 (1H, m), 6.59 (1H, d, J=8Hz), 6.62  
(1H, s), 6.74 (1H, d, J=8Hz), 6.87 (1H, d, J=8Hz),  
6.92 (1H, d, J=8Hz), 6.98 (1H, d, J=8Hz), 7.01 (1H,  
s), 7.10 (1H, t, J=8Hz), 8.25 (1H, d, J=8Hz), 8.39  
(1H, s)

- 4) 4-[(Indolin-6-yl)carbonyl]amino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide

20  
25  
NMR (CDCl<sub>3</sub>, δ) : 1.48-1.58 (2H, m), 1.64-1.87 (4H, m),  
2.28 (3H, s), 2.30 (3H, s), 2.32-2.42 (6H, m), 3.07  
(2H, t, J=8Hz), 3.32 (3H, s), 3.46-3.51 (2H, m),  
3.60 (2H, t, J=8Hz), 3.61-3.68 (2H, m), 3.77 (3H,  
s), 3.83-3.98 (2H, m), 6.58 (1H, d, J=8Hz), 6.62  
(1H, s), 6.84 (1H, d, J=8Hz), 6.91 (1H, d, J=8Hz),  
6.99-7.16 (3H, m), 8.27 (1H, d, J=8Hz), 8.44 (1H,  
s)

- 5) 4-[2-[[2-(Dimethylamino)ethyl]amino]-1H-benzimidazol-4-yl]carbonyl-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]-benzamide

30  
35  
NMR (DMSO-d<sub>6</sub>, δ) : 1.35-1.50 (2H, m), 1.50-1.66 (2H,  
m), 1.66-1.85 (2H, m), 2.14 (3H, s), 2.17-2.39  
(15H, m), 2.45-2.60 (2H, m), 3.21 (3H, s), 3.27-

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3.53 (6H, m), 3.80-4.01 (5H, m), 6.46-6.54 (1H, m),  
6.60-6.71 (1H, m), 6.72-6.85 (2H, m), 6.90 (1H, d,  
J=8Hz), 6.95-7.04 (3H, m), 7.81-7.94 (2H, m)

5     Example 47

The following compounds were obtained according to a  
similar manner to that of Example 25.

1) 4-[2-Carbamoyl-1H-benzimidazol-4-yl]carbonylamino-3-  
10 methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-  
yl)carbonylpent-1-yloxy]phenyl]benzamide  
NMR (CDCl<sub>3</sub>, δ) : 1.44-1.66 (2H, m), 1.66-1.80 (2H, m),  
1.80-1.93 (2H, m), 2.26 (3H, s), 2.30 (3H, s),  
2.32-2.46 (6H, m), 3.35 (3H, s), 3.45-3.54 (2H, m),  
15 3.60-3.71 (2H, m), 3.79-3.92 (4H, m), 3.92-4.03  
(1H, m), 6.32 (1H, br peak), 6.56-6.69 (2H, m),  
6.90 (1H, d, J=8Hz), 6.94-7.04 (1H, m), 7.10 (1H,  
s), 7.48-7.61 (2H, m), 7.73 (1H, d, J=8Hz), 8.28  
(1H, d, J=8Hz), 8.47-8.57 (1H, m)

20

2) 4-[2-(N,N-Dimethylcarbamoyl)-1H-benzimidazol-4-yl]-  
carbonylamino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-  
methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]-  
benzamide  
25 NMR (CDCl<sub>3</sub>, δ) : 1.45-1.64 (2H, m), 1.64-1.78 (2H, m),  
1.78-1.92 (2H, m), 2.26 (3H, s), 2.29 (3H, s),  
2.31-2.43 (6H, m), 3.25 (3H, s), 3.33 (3H, s),  
3.43-3.53 (2H, m), 3.59-3.68 (2H, m), 3.70-4.03  
(8H, m), 6.54-6.69 (2H, m), 6.86 (1H, d, J=8Hz),  
30 6.93 (1H, d, J=8Hz), 7.09 (1H, s), 7.49 (1H, br  
peak), 7.71 (1H, br peak), 8.25 (1H, br peak), 8.34  
(1H, d, J=8Hz)

35     Example 48

The following compounds were obtained according to a

similar manner to that of Example 26.

1) 4-(2-Aminomethyl-1H-benzimidazol-4-yl)carbonylamino-N-  
[2-(5-ethoxycarbonylpent-1-yloxy)-4-methoxyphenyl]-3-  
methoxy-N-methylbenzamide

2) 4-(2-Aminomethyl-1H-benzimidazol-4-yl)carbamoyl-3-  
methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-  
yl)carbonylpent-1-yloxy]phenyl]benzamide

NMR (DMSO-d<sub>6</sub>, δ) : 1.36-1.50 (2H, m), 1.50-1.64 (2H,  
m), 1.70-1.82 (2H, m), 2.15 (3H, s), 2.17-2.40 (9H,  
m), 3.21 (3H, s), 3.37-3.47 (4H, m), 3.81-4.04 (7H,  
m), 6.64 (1H, d, J=8Hz), 6.81 (1H, s), 6.99-7.14  
(4H, m), 7.14-7.24 (1H, m), 7.90 (1H, br peak),  
8.09 (1H, br peak)

3) 4-[2-(2-Aminoethyl)-1H-benzimidazol-4-yl]carbamoyl-3-  
methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-  
yl)carbonylpent-1-yloxy]phenyl]benzamide

NMR (DMSO-d<sub>6</sub>, δ) : 1.36-1.51 (2H, m), 1.51-1.64 (2H,  
m), 1.70-1.83 (2H, m), 2.14 (3H, s), 2.17-2.38 (9H,  
m), 2.94 (2H, t, J=5Hz), 3.09 (2H, t, J=5Hz), 3.21  
(3H, s), 3.24-3.49 (4H, m), 3.84-4.04 (5H, m), 6.64  
(1H, d, J=8Hz), 6.81 (1H, s), 7.02 (1H, d, J=8Hz),  
7.06-7.20 (4H, m), 7.85-7.94 (1H, m), 8.00-8.10  
(1H, m)

#### Example 49

The following compounds were obtained according to a  
similar manner to that of Example 28.

1) 4-(2-Amino-3-nitrobenzoyl)amino-N-[2-[4,4-dimethyl(2,5-  
oxazolinyl)]phenyl]-3-methoxy-N-methylbenzamide

NMR (CDCl<sub>3</sub>, δ) : 1.35 (6H, s), 3.39 (3H, s), 3.67 (3H,  
s), 4.09 (2H, s), 6.68 (1H, dd, J=8, 8Hz), 6.99

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(1H, s), 7.05 (1H, d, J=8Hz), 7.14 (1H, d, J=8Hz),  
7.27 (1H, dd, J=8, 8Hz), 7.37 (1H, dd, J=8, 8Hz),  
7.70 (1H, d, J=8Hz), 7.79 (1H, d, J=8Hz), 8.04-8.23  
(3H, m), 8.25-8.36 (2H, m)

5

- 2) 4-(2-Amino-3-nitrobenzoyl)amino-3-methoxy-N-methyl-N-[2-(morpholin-4-yl)phenyl]benzamide

NMR (CDCl<sub>3</sub>, δ) : 2.45-2.63 (2H, m), 2.80-2.98 (2H, m),  
3.49 (3H, s), 3.63-3.86 (7H, m), 6.69 (1H, dd, J=8,  
10 8Hz), 6.92 (1H, d, J=8Hz), 7.02 (1H, m), 7.05-7.16  
(2H, m), 7.17-7.30 (2H, m), 7.72 (1H, d, J=8Hz),  
8.10-8.22 (3H, m), 8.28-8.40 (2H, m)

- 3) 4-(2-Amino-3-nitrobenzoyl)amino-3-methoxy-N-methyl-N-(2-piperidinophenyl)benzamide

NMR (CDCl<sub>3</sub>, δ) : 1.43-1.72 (6H, m), 2.42-2.56 (2H, m),  
2.73-2.87 (2H, m), 3.50 (3H, s), 3.71 (3H, s), 6.68  
(1H, dd, J=8, 8Hz), 6.90 (1H, d, J=8Hz), 6.97-7.07  
(3H, m), 7.12-7.22 (2H, m), 7.73 (1H, d, J=8Hz),  
20 8.11-8.22 (3H, m), 8.28-8.39 (2H, m)

- 4) 4-(2-Amino-3-nitrobenzoyl)amino-3-methoxy-N-methyl-N-[2-(4-methyl-1-piperazinyl)phenyl]benzamide

NMR (CDCl<sub>3</sub>, δ) : 2.40 (3H, s), 2.45-2.73 (6H, m), 2.89-  
25 3.04 (2H, m), 3.50 (3H, s), 3.69 (3H, s), 6.68 (1H,  
dd, J=8, 8Hz), 6.89-7.01 (2H, m), 7.02-7.12 (2H,  
m), 7.15-7.29 (2H, m), 7.72 (1H, d, J=8Hz), 8.09-  
8.24 (3H, m), 8.28-8.38 (2H, m)

30 Example 50

The following compound was obtained according to a  
similar manner to that of Example 29.

4-(2-Carboxyphenylcarbamoyl)-3-methoxy-N-methyl-N-[4-  
35 methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]-



phenyl]benzamide

5 NMR (DMSO-d<sub>6</sub>, δ) : 1.38-1.65 (4H, m), 1.70-1.85 (2H, m), 2.21 (3H, s), 2.30-2.60 (6H, m), 2.68-2.91 (3H, m), 3.17 (3H, s), 3.20 (3H, s), 3.66 (3H, s), 3.83-4.03 (3H, m), 6.10 (1H, d, J=8Hz), 6.82-7.02 (3H, m), 7.43-7.52 (2H, m), 7.63-7.70 (2H, m), 7.91-8.01 (2H, m), 8.67 (1H, d, J=8Hz)

Example 51

10 The following compound was obtained by using 4-(1H-benzimidazol-4-yl)carbonylamino-N-(2-methoxycarbonyl-4-methylphenyl)-3-methoxy-N-methylbenzamide as a starting compound according to a similar manner to that of Example 29.

15 4-(1H-Benzimidazol-4-yl)carbonylamino-N-(2-carboxy-4-methylphenyl)-3-methoxy-N-methylbenzamide

20 NMR (DMSO-d<sub>6</sub>, δ) : 2.29 (3H, s), 3.28 (3H, s), 3.70 (3H, s), 6.80-6.89 (2H, m), 7.28-7.43 (3H, m), 7.51 (1H, s), 7.80 (1H, d, J=8Hz), 7.94 (1H, d, J=8Hz), 8.31 (1H, m), 8.53 (1H, s)

Example 52

25 The following compound was obtained according to a similar manner to that of Example 51.

N-(2-Carboxy-4-methylphenyl)-3-methoxy-N-methyl-4-(2-methyl-1H-benzimidazol-4-yl)carbonylaminobenzamide

30 NMR (DMSO-d<sub>6</sub>, δ) : 2.29 (3H, s), 2.65 (3H, s), 3.29 (3H, s), 3.73 (3H, s), 6.80-6.89 (2H, m), 7.28-7.38 (3H, m), 7.51 (1H, s), 7.70 (1H, d, J=8Hz), 7.89 (1H, d, J=8Hz), 8.30 (1H, br)

Example 53

35 The following compounds were obtained according to a similar manner to that of Example 30.

- 1) 4-[(2-Carbamoylindol-4-yl)carbonyl]amino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)-carbonylpent-1-yloxy]phenyl]benzamide

5 NMR (CDCl<sub>3</sub>, δ) : 1.47-1.56 (2H, m), 1.63-1.87 (4H, m),  
2.28 (3H, s), 2.29 (3H, s), 2.31-2.42 (6H, m), 3.33  
(3H, s), 3.47-3.51 (2H, m), 3.58-3.65 (2H, m), 3.74  
(3H, s), 3.85-4.00 (2H, m), 6.59-6.66 (2H, m), 6.91  
(1H, d, J=8Hz), 6.98-7.03 (2H, m), 7.35 (1H, t,  
J=8Hz), 7.52 (1H, d, J=8Hz), 7.57-7.63 (2H, m),  
10 8.32 (1H, d, J=8Hz), 8.60 (1H, s), 9.88 (1H, s)

- 2) 4-[[2-(N-Methylcarbamoyl)indol-4-yl]carbonyl]amino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide

15 NMR (CDCl<sub>3</sub>, δ) : 1.45-1.56 (2H, m), 1.63-1.86 (4H, m),  
2.27 (3H, s), 2.29 (3H, s), 2.30-2.42 (6H, m), 3.04  
and 3.06 (Total 3H, s), 3.34 (3H, s), 3.47-3.52  
(2H, m), 3.57-3.63 (2H, m), 3.75 (3H, s), 3.83-4.00  
(2H, m), 6.58-6.64 (2H, m), 6.90 (1H, d, J=8Hz),  
20 6.98-7.03 (2H, m), 7.32 (1H, t, J=8Hz), 7.46 (1H,  
s), 7.51 (1H, d, J=8Hz), 7.60 (1H, d, J=8Hz), 8.02  
(1H, s), 8.33 (1H, d, J=8Hz), 8.59 (1H, s), 9.76  
(1H, s)

- 25 3) 4-[2-(N,N-Dimethylcarbamoyl)phenylcarbamoyl]-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide

30 NMR (CDCl<sub>3</sub>, δ) : 1.49-1.59 (2H, m), 1.67-1.89 (4H, m),  
2.27 (3H, s), 2.30 (3H, s), 2.32-2.42 (6H, m), 2.93  
(3H, s), 3.12 (3H, s), 3.35 (3H, s), 3.47-3.52 (2H,  
m), 3.60-3.67 (2H, m), 3.84-3.98 (2H, m), 3.92 (3H,  
s), 6.58 (1H, d, J=8Hz), 6.61 (1H, s), 6.83 (1H, d,  
J=8Hz), 6.98 (1H, d, J=8Hz), 7.01 (1H, s), 7.10  
(1H, t, J=8Hz), 7.20 (1H, d, J=8Hz), 7.40 (1H, t,  
J=8Hz), 8.01 (1H, d, J=8Hz), 8.39 (1H, d, J=8Hz)

35

Example 54

The following compounds were obtained according to a similar manner to that of Example 32.

- 5      1) 4-[(1-tert-Butoxycarbonyl-3-hydroxymethylindol-4-yl)-  
carbonyl]amino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-  
methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]-  
benzamide

10            NMR (CDCl<sub>3</sub>, δ) : 1.49-1.61 (2H, m), 1.66 (9H, s), 1.67-  
1.89 (4H, m), 2.29 (3H, s), 2.30 (3H, s), 2.32-2.42  
(6H, m), 3.34 (3H, s), 3.46-3.51 (2H, m), 3.60-3.67  
(2H, m), 3.76 (3H, s), 3.88-4.01 (2H, m), 4.61 (2H,  
s), 6.61 (1H, d, J=8Hz), 6.67 (1H, s), 6.87 (1H, d,  
J=8Hz), 6.93 (1H, d, J=8Hz), 7.07 (1H, s), 7.37  
15            (1H, t, J=8Hz), 7.44 (1H, d, J=8Hz), 7.68 (1H, s),  
8.29 (1H, d, J=8Hz), 8.39-8.47 (2H, m)

- 20      2) 4-(2-Hydroxymethyl-1H-benzimidazol-4-yl)carbamoyl-3-  
methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-  
yl)carbonylpent-1-yloxy]phenyl]benzamide

25            NMR (DMSO-d<sub>6</sub>, δ) : 1.40-1.50 (2H, m), 1.50-1.63 (2H, m),  
1.69-1.82 (2H, m), 2.14 (3H, s), 2.17-2.37 (9H, m),  
3.21 (3H, s), 3.37-3.48 (4H, m), 3.83-4.03 (5H, m),  
4.72 (2H, d, J=5Hz), 5.74 (1H, br peak), 6.64 (1H,  
d, J=8Hz), 6.80 (1H, s), 6.99-7.23 (5H, m), 7.90  
             (1H, d, J=8Hz), 8.09 (1H, d, J=8Hz)

Example 55

30      The following compounds were obtained according to  
similar manners to those of Examples 4 and 28.

- 1) 4-(2-Amino-3-nitrophenyl)carbonylamino-3-methoxy-N-(2-  
methoxycarbonyl-4-methylphenyl)-N-methylbenzamide

35            NMR (CDCl<sub>3</sub>, δ) : 2.23 (3H, s), 3.39 (3H, s), 3.75 (3H,  
s), 3.89 (3H, s), 6.67 (1H, t, J=8Hz), 6.83 (1H, d,

J=8Hz), 6.97 (1H, s), 7.12 (1H, d, J=8Hz), 7.27 (1H, d, J=8Hz), 7.59 (1H, s), 7.70 (1H, d, J=8Hz), 8.04-8.18 (3H, m), 8.12 (1H, d, J=8Hz)

- 5        2) 4-(2-Amino-3-nitrophenyl)carbonylamino-3-methoxy-N-[2-(4-methoxyphenylmethyloxy)-4-methylphenyl]-N-methylbenzamide

10        NMR (CDCl<sub>3</sub>, δ) : 2.28 (3H, s), 3.37 (3H, s), 3.66 (3H, s), 3.81 (3H, s), 4.87 (1H, d, J=12Hz), 5.01 (1H, d, J=12Hz), 6.60-6.73 (3H, m), 6.85-6.99 (4H, m), 7.23-7.31 (3H, m), 7.71 (1H, d, J=8Hz), 8.10-8.19 (3H, m), 8.29-8.34 (2H, m)

- 15        3) 4-(2-Amino-3-nitrophenyl)carbonylamino-3-methoxy-N-methyl-N-[2-(5-tert-butoxycarbonylamino-pent-1-yl)oxy-4-methyl]phenylbenzamide

20        NMR (CDCl<sub>3</sub>, δ) : 1.41 (9H, s), 1.45-1.60 (4H, m), 1.75-1.84 (2H, m), 2.28 (3H, s), 3.09-3.18 (2H, m), 3.31 (3H, s), 3.78 (3H, s), 3.80-3.97 (2H, m), 4.67 (1H, br), 6.58-6.63 (2H, m), 6.69 (1H, t, J=8Hz), 6.89 (1H, d, J=8Hz), 6.96 (1H, d, J=8Hz), 7.03 (1H, s), 7.71 (1H, d, J=8Hz), 8.13 (1H, d, J=8Hz), 8.29-8.37 (3H, m)

25        Example 56

The following compounds were obtained according to similar manners to those of Examples 7 and 16.

- 30        1) N-(2-Amino-4-methylphenyl)-3-methoxy-N-methyl-4-(2-methyl-1H-benzimidazol-4-yl)carbonylamino-benzamide

35        NMR (CDCl<sub>3</sub>, δ) : 2.18 (3H, s), 2.76 (3H, s), 3.31 (3H, s), 3.80 (3H, s), 6.37 (1H, d, J=8Hz), 6.53 (1H, s), 6.66 (1H, d, J=8Hz), 7.00-7.08 (2H, m), 7.26 (1H, t, J=8Hz), 7.60 (1H, d, J=8Hz), 7.86 (1H, br), 8.44 (1H, d, J=8Hz)

- 2) 3-Methoxy-N-methyl-4-(2-methyl-1H-benzimidazol-4-yl)carbonylamino-N-[2-(5-tert-butoxycarbonylamino-pent-1-yl)oxy-4-methyl]phenylbenzamide

NMR (CDCl<sub>3</sub>, δ) : 1.42 (9H, s), 1.42-1.60 (4H, m), 1.72-1.85 (2H, m), 2.28 (3H, s), 2.67 (3H, s), 3.08-3.17 (2H, m), 3.36 (3H, s), 3.60-3.97 (2H, m), 3.78 (3H, s), 4.80 (1H, br), 6.57-6.63 (2H, m), 6.80-7.08 (3H, m), 7.30 (1H, m), 7.59 (1H, m), 7.91 (1H, br), 8.45 (1H, m)

- 3) N-[2-[4,4-Dimethyl(2,5-oxazolinyl)]phenyl]-3-methoxy-N-methyl-4-(2-methyl-1H-benzimidazol-4-yl)-carbonylamino-benzamide

NMR (CDCl<sub>3</sub>, δ) : 1.33 (3H, s), 1.35 (3H, s), 1.60 (3H, s), 3.41 (3H, s), 3.68 (3H, s), 4.04-4.14 (2H, m), 6.95 (1H, s), 7.07 (1H, d, J=8Hz), 7.14 (1H, d, J=8Hz), 7.18-7.39 (4H, m), 7.59 (1H, d, J=8Hz), 7.80 (1H, d, J=8Hz), 7.90 (1H, d, J=8Hz), 8.47 (1H, d, J=8Hz)

- 4) 3-Methoxy-N-methyl-4-(2-methyl-1H-benzimidazol-4-yl)carbonylamino-N-[2-(morpholin-4-yl)phenyl]benzamide

NMR (DMSO-d<sub>6</sub>, δ) : 2.25-2.44 (2H, m), 2.62 (3H, s), 2.72-2.90 (2H, m), 3.20-3.80 (10H, m), 6.87-6.99 (2H, m), 7.05 (1H, d, J=8Hz), 7.09-7.26 (2H, m), 7.30 (1H, dd, J=8, 8Hz), 7.42 (1H, d, J=8Hz), 7.67 (1H, d, J=8Hz), 7.87 (1H, d, J=8Hz), 8.41 (1H, m)

- 5) 3-Methoxy-N-methyl-4-(2-methyl-1H-benzimidazol-4-yl)carbonylamino-N-(2-piperidinophenyl)benzamide

NMR (CDCl<sub>3</sub>, δ) : 1.41-1.72 (6H, m), 2.36-2.53 (2H, m), 2.66 (3H, s), 2.70-2.87 (2H, m), 3.51 (3H, s), 3.71 (3H, s), 6.88 (1H, d, J=8Hz), 6.93-7.33 (7H, m), 7.62 (1H, d, J=8Hz), 7.90 (1H, d, J=8Hz), 8.42 (1H, d, J=8Hz)

- 6) 3-Methoxy-N-methyl-4-(2-methyl-1H-benzimidazol-4-yl)-  
carbonylamino-N-[2-(4-methyl-1-piperazinyl)phenyl]-  
benzamide

5 NMR (CDCl<sub>3</sub>, δ) : 2.40 (3H, br s), 2.46-2.70 (9H, m),  
2.86-3.01 (2H, m), 3.51 (3H, s), 3.70 (3H, s),  
6.82-6.98 (2H, m), 7.02-7.21 (3H, m), 7.22-7.36  
(2H, m), 7.43-7.54 (1H, m), 8.11 (1H, d, J=8Hz),  
8.58 (1H, d, J=8Hz)

10 Example 57

To a solution of 2-(4-pyridyl)-1H-benzimidazole-4-  
carboxylic acid (155 mg) in dichloromethane (2 ml) was added  
oxalyl chloride (0.056 ml) and N,N-dimethylformamide (2  
drops) and stirred at ambient temperature for 2 hours. The  
15 reaction mixture was concentrated in vacuo to give 2-(4-  
pyridyl)-1H-benzimidazole-4-carbonyl chloride. To a solution  
of 4-amino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-  
methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide  
(76.8 mg) and triethylamine (65 mg) in dichloromethane (5 ml)  
20 was added 2-(4-pyridyl)-1H-benzimidazole-4-carbonyl chloride  
in dichloromethane (2 ml) under ice bath cooling and stirred  
at ambient temperature for 6 hours. After the reaction  
mixture was concentrated in vacuo, the residue was diluted  
with chloroform and saturated sodium hydrogen carbonate  
25 aqueous solution. The organic layer was separated and washed  
with brine. The solution was dried over magnesium sulfate  
and concentrated in vacuo. The residue was purified by  
silica gel (Chromatorex, Fuji Silysia Chemical Ltd.) column  
chromatography (methanol:chloroform = 1:49). To the purified  
30 product was added water and 1N hydrochloric acid (0.51 ml).  
The solution was lyophilized to give 3-methoxy-N-methyl-N-[4-  
methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]-  
phenyl]-4-[2-(4-pyridyl)-1H-benzimidazol-4-yl]carbonylamino-  
benzamide trihydrochloride (120 mg).

35 NMR (DMSO-d<sub>6</sub>, δ) : 1.42-1.52 (2H, m), 1.52-1.62 (2H,

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5 m), 1.73-1.83 (2H, m), 2.22 (3H, s), 2.41 (2H, t, J=7Hz), 2.73 (3H, s), 2.82-3.07 (4H, m), 3.21 (3H, s), 3.32-3.52 (3H, m), 3.88 (3H, s), 3.90-4.13 (2H, m), 4.40-4.50 (1H, m), 6.66 (1H, d, J=8Hz), 6.83 (1H, s), 6.98 (1H, d, J=8Hz), 7.03 (1H, s), 7.07 (1H, d, J=8Hz), 7.55 (1H, t, J=8Hz), 7.94 (1H, d, J=8Hz), 8.07 (1H, d, J=8Hz), 8.48 (1H, d, J=8Hz), 8.75 (2H, br s)

10 Example 58

The following compounds were obtained according to a similar manner to that of Example 57.

15 1) 3-Methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]-4-[2-(3-pyridyl)-1H-benzimidazol-4-yl]carbonylaminobenzamide trihydrochloride

20 NMR (DMSO-d<sub>6</sub>, δ) : 1.40-1.52 (2H, m), 1.52-1.65 (2H, m), 1.70-1.83 (2H, m), 2.22 (3H, s), 2.40 (2H, t, J=7Hz), 2.73 (3H, s), 2.85-3.12 (4H, m), 3.21 (3H, s), 3.35-3.53 (3H, m), 3.88 (3H, s), 3.92-4.13 (2H, m), 4.40-4.45 (1H, m), 6.66 (1H, d, J=8Hz), 6.83 (1H, s), 6.96 (1H, d, J=8Hz), 7.01 (1H, s), 7.06 (1H, d, J=8Hz), 7.48 (1H, t, J=8Hz), 7.89 (1H, d, J=8Hz), 8.03 (1H, d, J=8Hz), 8.13 (1H, t, J=8Hz), 8.48 (1H, d, J=8Hz), 9.00 (1H, br s), 9.12 (1H, d, J=8Hz), 9.67 (1H, br s)

30 2) 3-Methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]-4-[2-(2-pyridyl)-1H-benzimidazol-4-yl]carbonylaminobenzamide trihydrochloride

35 NMR (DMSO-d<sub>6</sub>, δ) : 1.40-1.52 (2H, m), 1.52-1.63 (2H, m), 1.68-1.82 (2H, m), 2.22 (3H, s), 2.37 (2H, t, J=7Hz), 2.72 (3H, s), 2.82-3.10 (4H, m), 3.20 (3H,

5 s), 3.33-3.56 (3H, m), 3.85 (3H, s), 3.90-4.10 (2H, m), 4.40-4.45 (1H, m), 6.62 (1H, t, J=8Hz), 6.80-7.06 (4H, m), 7.43 (1H, t, J=8Hz), 7.63 (1H, t, J=7Hz), 7.79 (1H, d, J=8Hz), 7.98 (1H, d, J=8Hz), 8.17 (1H, t, J=8Hz), 8.48 (1H, t, J=8Hz), 8.82 (1H, d, J=5Hz)

10 3) 4-(2H-1,4-Benzoxazin-3-oxo-8-yl)carbonylamino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)-carbonylpent-1-yloxy]phenyl]benzamide hydrochloride  
NMR (DMSO-d<sub>6</sub>, δ) : 1.40-1.51 (2H, m), 1.51-1.63 (2H, m), 1.70-1.80 (2H, m), 2.22 (3H, s), 2.37 (2H, t, J=7Hz), 2.73 (3H, s), 2.80-3.04 (4H, m), 3.17 (3H, s), 3.36-3.50 (3H, m), 3.73 (3H, s), 3.80-4.15 (2H, m), 4.40-4.47 (1H, m), 4.89 (2H, s), 6.64 (1H, d, J=8Hz), 6.80 (1H, s), 6.88-6.93 (2H, m), 7.03 (1H, d, J=8Hz), 7.10-7.13 (2H, m), 7.59-7.62 (1H, m), 8.22 (1H, d, J=8Hz)

20 Example 59

The following compound was obtained by using N-(2-phthalimido-4-methylphenyl)-2-amino-3-methoxy-N-methylbenzamide as a starting compound according to a similar manner to that of Example 4.

25

N-(2-Amino-4-methylphenyl)-4-(2-amino-3-nitrophenyl)carbonylamino-3-methoxy-N-methylbenzamide

30 NMR (CDCl<sub>3</sub>, δ) : 2.20 (3H, s), 3.30 (3H, s), 3.79 (3H, s), 3.89 (2H, br s), 6.39 (1H, d, J=8Hz), 6.52 (1H, s), 6.63-6.71 (2H, m), 7.05 (1H, d, J=8Hz), 7.10 (1H, s), 7.70 (1H, d, J=8Hz), 8.12 (2H, br s), 8.20 (1H, d, J=8Hz), 8.31 (1H, d, J=8Hz), 8.34 (1H, br)

Example 60

35 A mixture of N-[2-(5-ethoxycarbonylpent-1-yloxy)-4-



methoxyphenyl]-3-methoxy-N-methyl-4-(3-nitro-2-phthalimidomethylcarbonylaminophenyl)carbonylaminobenzamide (3.96 g), iron powder (1.42 g) and acetic acid (3.05 g) in ethanol (50 ml) was refluxed for 4 hours and the solvent was removed under reduce pressure. The residue was stirred in a mixture of chloroform (100 ml) and saturated aqueous sodium hydrogen carbonate (100 ml) for 30 minutes and the solution was filtered through a bed of celite. The organic phase was separated and washed with brine. The solution was dried over magnesium sulfate and the solvent was evaporated in vacuo. The residue was solidified with diethyl ether to give N-[2-(5-ethoxycarbonylpent-1-yloxy)-4-methylphenyl]-3-methoxy-N-methyl-4-(2-phthalimidomethyl-1H-benzimidazol-4-yl)-carbonylaminobenzamide (3.64 g).

NMR (CDCl<sub>3</sub>, δ) : 1.24 (3H, t, J=7.5Hz), 1.46-1.57 (2H, m), 1.63-1.75 (2H, m), 1.75-1.88 (2H, m), 2.25 (3H, s), 2.34 (2H, t, J=7.5Hz), 3.31 (3H, s), 3.74-4.00 (2H, m), 4.02 (3H, s), 4.12 (2H, q, J=7.5Hz), 5.21 (2H, s), 6.53-6.63 (2H, m), 6.86 (1H, d, J=8Hz), 6.93 (1H, d, J=8Hz), 7.03 (1H, s), 7.35 (1H, t, J=8Hz), 7.53 (1H, d, J=8Hz), 7.68-7.78 (2H, m), 7.84-7.93 (2H, m), 8.14 (1H, d, J=8Hz), 8.50 (1H, d, J=8Hz)

#### 25 Example 61

To a solution of 4-(2,3-diaminobenzoyl)amino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)-carbonylpent-1-yloxy]phenyl]benzamide (240 mg) in acetonitrile (1 ml) was added cyanoacetic acid (662 mg). The solution was heated at 100°C for 8 hours. After cooling, aqueous sodium hydrogen carbonate was added to the mixture and extracted with ethyl acetate. The extract was washed with brine and dried over sodium sulfate. After evaporation of the solvent, the residue was purified by silica gel column chromatography (7% methanol in chloroform) and preparative

thin-layer chromatography (ethyl acetate:methanol = 1:1) to give 4-[[2-cyanomethyl-1H-benzimidazol-4-yl]carbonylamino]-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide (80 mg).

5       NMR (CDCl<sub>3</sub>, δ) : 1.42-1.94 (6H, m), 2.24 (3H, s), 2.29 (3H, s), 2.32-2.48 (6H, m), 3.36 (3H, s), 3.43-3.55 (2H, m), 3.55-4.21 (9H, m), 6.50-6.68 (2H, m), 6.78 (1H, br), 6.81-7.02 (2H, m), 7.20-7.31 (1H, m), 7.36-7.48 (1H, m), 8.08 (1H, d, J=8Hz), 8.47 (1H, d, J=8Hz)

10

#### Example 62

A solution of 4-(2,3-diaminobenzoyl)amino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide (100 mg) and mercaptoacetic acid (448 mg) was heated at 80°C for 5 hours. The reaction mixture was diluted with chloroform and washed with aqueous sodium hydrogen carbonate. The extract was dried over sodium sulfate. After evaporation of the solvent, the residue was purified by silica gel column chromatography (10% methanol in chloroform) to give 3-methoxy-4-(2-mercaptomethyl-1H-benzimidazol-4-yl)carbonylamino-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide (60 mg).

15

20

25       NMR (CDCl<sub>3</sub>, δ) : 1.42-1.90 (6H, m), 2.19-2.47 (12H, m), 3.34 (3H, s), 3.49 (2H, m), 3.57-4.07 (9H, m), 6.51-6.68 (2H, m), 6.81-7.05 (3H, m), 7.31 (1H, dd, J=8, 8Hz), 7.51 (1H, d, J=8Hz), 8.12 (1H, d, J=8Hz), 8.50 (1H, m)

30

#### Example 63

A solution of 4-(2,3-diaminobenzoyl)amino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide (150 mg), butyrolactone (628 mg) and p-toluenesulfonic acid (139 mg) was heated at 100°C for 4

35

hours. The reaction mixture was diluted with chloroform and washed with aqueous sodium hydrogen carbonate. The extract was dried over sodium sulfate. After evaporation of the solvent, the residue was purified by silica gel column chromatography (10% methanol in chloroform) and then preparative thin-layer chromatography (chloroform/methanol = 20/3) to give 4-[2-(3-hydroxypropyl)-1H-benzimidazol-4-yl]carbonylamino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide (70 mg).

NMR (CDCl<sub>3</sub>, δ) : 1.44-1.59 (2H, m), 1.63-1.88 (4H, m), 2.01-2.14 (2H, m), 2.25 (3H, s), 2.27 (3H, s), 2.30-2.43 (6H, m), 2.90-3.03 (2H, m), 3.34 (3H, s), 3.42-3.52 (2H, m), 3.56-4.02 (9H, m), 6.52-6.66 (2H, m), 6.78-7.03 (3H, m), 7.24 (1H, dd, J=8, 8Hz), 7.46 (1H, m), 8.07 (1H, m), 8.52 (1H, m)

#### Example 64

To a mixture of 4-(2,3-diaminobenzoyl)amino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide (140 mg) and sodium carbonate (14 mg) in ethyl acetate (1.5 ml) was added dropwise a solution of 1,1-dichloro-1,1-diphenoxymethane (67 mg) in ethyl acetate (1 ml) in water bath and the mixture was stirred at same temperature for 5 hours. The reaction mixture was evaporated in vacuo and dissolved in chloroform. The organic layer was washed with water, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by preparative thin-layer chromatography (chloroform:methanol = 10:1) to give 3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]-4-(2-phenoxy-1H-benzimidazol-4-yl)carbonylaminobenzamide (18 mg).

NMR (DMSO-d<sub>6</sub>, δ) : 1.33-1.48 (2H, m), 1.48-1.62 (2H, m), 1.62-1.78 (2H, m), 2.14 (3H, s), 2.17-2.35 (9H, m), 3.09 (3H, s), 3.17 (3H, s), 3.36-3.45 (4H, m),

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3.76-3.87 (1H, m), 3.87-3.99 (1H, m), 6.64 (1H, d, J=8Hz), 6.75 (1H, s), 6.81 (1H, s), 6.88 (1H, d, J=8Hz), 7.00 (1H, d, J=8Hz), 7.25-7.38 (2H, m), 7.45-7.52 (4H, m), 7.60 (1H, d, J=8Hz), 7.88 (1H, d, J=8Hz), 8.25 (1H, d, J=8Hz)

#### Example 65

A mixture of 4-(2,3-diaminobenzoyl)amino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide (150 mg) and diphenyl N-sulfamoylcarbonimide (85 mg) in dichloromethane (8 ml) was refluxed for 24 hours under nitrogen. The reaction mixture was poured into water and extracted with chloroform. The organic layer was washed with water, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by preparative thin-layer chromatography (chloroform:methanol = 10:1/chloroform:methanol = 6:1) to give 3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]-4-(2-sulfamoylamino-1H-benzimidazol-4-yl)-carbonylaminobenzamide (38 mg).

NMR (DMSO-d<sub>6</sub>, δ) : 1.37-1.50 (2H, m), 1.50-1.64 (2H, m), 1.64-1.82 (2H, m), 2.23 (6H, s), 2.27-2.43 (6H, m), 3.19 (3H, s), 3.40-3.51 (4H, m), 3.70 (3H, s), 3.80-4.03 (2H, m), 6.30 (2H, br peak), 6.65 (1H, d, J=8Hz), 6.82 (1H, s), 6.86-6.95 (2H, m), 7.03 (1H, d, J=8Hz), 7.07 (1H, t, J=8Hz), 7.32 (1H, d, J=8Hz), 7.70 (1H, d, J=8Hz), 7.91 (1H, br peak), 10.48 (1H, br peak), 11.49 (1H, br peak)

#### Example 66

A suspension of 4-(2,3-diaminobenzoyl)amino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide (150 mg) and diphenyl N-cyanocarbonimide (64 mg) in 2-propanol (2 ml) was refluxed for 3 hours under nitrogen. The reaction mixture was

evaporated in vacuo and dissolved in chloroform. The organic solution was washed with water, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by preparative thin-layer chromatography (chloroform:ethyl acetate:methanol = 8:1:1/chloroform:methanol = 10:1) to give 4-(2-cyanoamino-1H-benzimidazol-4-yl)carbonylamino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)-carbonylpent-1-yloxy]phenyl]benzamide (45 mg).

5 NMR (DMSO-d<sub>6</sub>, δ) : 1.38-1.51 (2H, m), 1.51-1.66 (2H, m), 1.66-1.81 (2H, m), 2.23 (3H, s), 2.35 (2H, t, J=7Hz), 2.60 (2H, br s), 2.80-2.99 (4H, m), 3.20 (3H, s), 3.50-3.68 (2H, m), 3.74-3.90 (3H, m), 3.90-4.02 (1H, m), 6.65 (1H, d, J=8Hz), 6.80-6.95 (4H, m), 7.03 (1H, d, J=8Hz), 7.07 (1H, d, J=8Hz),  
10 7.55 (1H, d, J=8Hz), 8.29-8.40 (1H, m)  
15

#### Example 67

A mixture of 4-(2,3-diaminophenyl)carbonylamino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide (200 mg), glyoxal (47 mg) and sodium hydrogen sulfite (169 mg) in ethanol (15 ml) was refluxed for 5 hours. The solution was diluted with chloroform (30 ml) and the solution was washed with water and brine. The organic solution was dried over magnesium sulfate  
20 and the solvent was evaporated in vacuo to give an oil. The crude product was purified by silica gel column (1% methanol in chloroform) to give 3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]-4-(quinoxalin-5-yl)carbonylaminobenzamide (131 mg).

30 NMR (CDCl<sub>3</sub>, δ) : 1.49-1.60 (2H, m), 1.63-1.77 (2H, m), 1.77-1.90 (2H, m), 2.27 (3H, s), 2.32 (3H, s), 2.33-2.46 (6H, m), 3.31 (3H, s), 3.45-3.53 (2H, m), 3.60-3.69 (2H, m), 3.74-4.00 (2H, m), 3.81 (3H, s), 6.54-6.66 (2H, m), 6.87 (1H, d, J=8Hz), 6.98 (1H, d, J=8Hz), 7.06 (1H, s), 8.18-8.27 (3H, m), 8.52  
35

(1H, s), 8.75 (1H, s), 8.93 (2H, s)

#### Example 68

To a solution of 4-[N-[1-[(tert-butyl)oxycarbonyl]-  
5 benzimidazol-4-yl]carbamoyl]-N-[2-[4,4-dimethyl(2,5-  
oxazolinyl)]phenyl]-3-methoxy-N-methylbenzamide (400 mg) in  
dichloromethane (10 ml) was added trifluoroacetic acid (4  
ml). The mixture was stirred at ambient temperature for 3  
hours. The reaction mixture was concentrated in vacuo and  
10 the residue was diluted with a mixture of chloroform and  
saturated aqueous sodium bicarbonate solution. The organic  
layer was separated and washed with water and brine. The  
solution was dried over magnesium sulfate and the solvent was  
evaporated in vacuo. The residue was purified by column  
15 chromatography (chloroform:methanol = 100:3) to give 4-[N-  
(1H-benzimidazol-4-yl)carbamoyl]-N-[2-[4,4-dimethyl(2,5-  
oxazolinyl)]phenyl]-3-methoxy-N-methylbenzamide (290 mg).

NMR (CDCl<sub>3</sub>, δ) : 1.38 (3H, s), 1.39 (3H, s), 3.40 (3H,  
s), 3.84 (3H, s), 4.01-4.17 (2H, m), 7.05-7.45 (7H,  
20 m), 7.62 (1H, d, J=8Hz), 7.79 (1H, d, J=8Hz), 7.96  
(1H, s), 8.07 (1H, d, J=8Hz)

#### Example 69

The following compounds were obtained according to a  
25 similar manner to that of Example 68.

- 1) 4-[N-(1H-Benzimidazol-4-yl)carbamoyl]-3-methoxy-N-  
methyl-N-[2-(morpholin-4-yl)phenyl]benzamide

NMR (CDCl<sub>3</sub>, δ) : 2.30-2.48 (2H, m), 2.77-2.94 (2H, m),  
30 3.52 (3H, s), 3.60-3.94 (7H, m), 6.75-7.37 (9H, m),  
7.59-8.43 (3H, m)

- 2) 4-[N-(1H-Benzimidazol-4-yl)carbamoyl]-3-methoxy-N-  
methyl-N-[2-(1-pyrrolyl)phenyl]benzamide

35 NMR (CDCl<sub>3</sub>, δ) : 3.50 (3H, s), 3.91 (3H, s), 6.21-6.30

(2H, m), 6.38-6.46 (2H, m), 6.56-6.68 (2H, m),  
7.06-7.53 (7H, m), 7.87-8.07 (2H, m)

- 3) 3-Methoxy-N-methyl-4-[N-(2-methyl-1H-benzimidazol-4-yl)carbamoyl]-N-[2-(4-methyl-1-piperazinyl)phenyl]-benzamide

NMR (CDCl<sub>3</sub>, δ) : 2.39 (3H, s), 2.41-2.68 (9H, m), 2.86-3.01 (2H, m), 3.52 (3H, s), 3.84 (3H, s), 6.89 (1H, d, J=8Hz), 6.99 (1H, s), 7.07-7.36 (7H, m), 8.10 (1H, d, J=8Hz)

- 4) 3-Methoxy-N-methyl-4-[N-(2-methyl-1H-benzimidazol-4-yl)carbamoyl]-N-[2-(2,5-oxazolyl)phenyl]benzamide

NMR (CDCl<sub>3</sub>, δ) : 2.60 (3H, s), 3.48 (3H, s), 3.80 (3H, s), 6.78-6.87 (2H, m), 7.13 (1H, dd, J=8, 8Hz), 7.28-7.47 (7H, m), 7.78 (1H, s), 7.88 (1H, m), 7.95 (1H, d, J=8Hz)

#### Example 70

The solution of 4-[(1-tert-butoxycarbonyl-2-phthalimido-methylindol-4-yl)carbonyl]amino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]-phenyl]benzamide (312 mg) in ethanol (5.0 ml) and 1N sodium hydroxide aqueous solution (1.76 ml) was stirred at ambient temperature for 6 hours. The resulting solution was diluted with water and extracted with chloroform. The organic layer was dried over magnesium sulfate and concentrated in vacuo to afford 4-[(2-aminomethylindol-4-yl)carbonyl]amino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide (228 mg).

NMR (DMSO-d<sub>6</sub>, δ) : 1.38-1.62 (4H, m), 1.68-1.80 (2H, m), 2.15 (3H, s), 2.18-2.37 (6H, m), 2.23 (3H, s), 3.19 (3H, s), 3.26-3.48 (3H, m), 3.69 (3H, s), 3.80-4.01 (3H, m), 4.18 (2H, s), 6.67 (1H, d, J=8Hz), 6.83 (1H, s), 6.90-6.98 (2H, m), 7.14 (1H,

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d, J=8Hz), 7.20 (1H, t, J=9Hz), 7.56 (1H, d, J=9Hz), 7.62 (1H, d, J=9Hz), 7.95 (1H, d, J=8Hz), 9.06 (1H, s)

5     Example 71

The following compounds were obtained according to a similar manner to that of Example 70.

- 1) 4-[(2-Methylindol-4-yl)carbonyl]amino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide

NMR (CDCl<sub>3</sub>, δ) : 1.46-1.60 (2H, m), 1.66-1.88 (4H, m), 2.28 (6H, s), 2.32-2.42 (6H, m), 2.48 (3H, s), 3.33 (3H, s), 3.44-3.51 (2H, m), 3.58-3.67 (2H, m), 3.78 (3H, s), 3.85-4.00 (2H, m), 6.59 (1H, d, J=8Hz), 6.63 (1H, s), 6.70 (1H, s), 6.87 (1H, d, J=8Hz), 6.93 (1H, d, J=8Hz), 7.04 (1H, s), 7.17 (1H, t, J=8Hz), 7.42 (1H, d, J=8Hz), 7.57 (1H, d, J=8Hz), 8.30-8.40 (2H, m), 8.71 (1H, s)

- 2) 4-[(3-Hydroxymethylindol-4-yl)carbonyl]amino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)-carbonylpent-1-yloxy]phenyl]benzamide

NMR (CDCl<sub>3</sub>, δ) : 1.49-1.89 (6H, m), 2.29 (3H, s), 2.30 (3H, s), 2.32-2.42 (6H, m), 3.34 (3H, s), 3.46-3.51 (2H, m), 3.60-3.66 (2H, m), 3.77 (3H, s), 3.89-4.00 (2H, m), 4.68 (2H, s), 6.62 (1H, d, J=8Hz), 6.67 (1H, s), 6.87 (1H, d, J=8Hz), 6.92 (1H, d, J=8Hz), 7.07 (1H, s), 7.22 (1H, t, J=8Hz), 7.29 (1H, s), 7.36 (1H, d, J=8Hz), 7.52 (1H, d, J=8Hz), 8.32 (1H, d, J=8Hz), 8.48-8.52 (2H, br s)

- 3) 4-[(Indol-6-yl)carbonyl]amino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide



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NMR (CDCl<sub>3</sub>, δ) : 1.47-1.58 (2H, m), 1.65-1.87 (4H, m),  
2.28 (3H, s), 2.29 (3H, s), 2.31-2.41 (6H, m), 3.33  
(3H, s), 3.45-3.51 (2H, m), 3.59-3.67 (2H, m), 3.77  
(3H, s), 3.83-3.99 (2H, m), 6.58-6.64 (3H, m), 6.88  
5 (1H, d, J=8Hz), 6.94 (1H, d, J=8Hz), 7.03 (1H, s),  
7.37 (1H, t, J=3Hz), 7.50 (1H, d, J=9Hz), 7.68 (1H,  
d, J=9Hz), 7.98 (1H, s), 8.32 (1H, d, J=8Hz), 8.60  
(1H, s), 8.83-8.88 (1H, br s)

10 Example 72

The following compound was obtained by using 3-methoxy-  
N-methyl-4-[2-[[2-(N-tert-butoxycarbonyl)methylamino]ethyl]-  
amino-1-tert-butoxycarbonyl-1H-benzimidazol-4-yl]carbamoyl-N-  
[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-  
15 yloxy]phenyl]benzamide as a starting compound according to a  
similar manner to that of Example 23.

3-Methoxy-N-methyl-4-[2-[[2-(methylamino)ethyl]amino]-  
1H-benzimidazol-4-yl]carbamoyl-N-[4-methyl-2-[5-(4-  
20 methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide  
NMR (CDCl<sub>3</sub>, δ) : 1.36-1.50 (2H, m), 1.50-1.64 (2H, m),  
1.64-1.82 (2H, m), 2.15 (3H, s), 2.17-2.36 (9H, m),  
2.40 (3H, s), 2.88 (2H, t, J=5Hz), 3.22 (3H, s),  
3.25-3.55 (7H, m), 3.81-4.02 (5H, m), 6.64 (1H, d,  
25 J=8Hz), 6.70-6.85 (3H, m), 6.90 (1H, d, J=8Hz),  
7.00 (1H, d, J=8Hz), 7.03-7.13 (2H, m), 7.77-7.90  
(2H, m)

Example 73

30 The following compound was obtained according to a  
similar manner to that of Example 72.

4-[2-[(2-Aminoethyl)methylamino]-1H-benzimidazol-4-yl]-  
carbamoyl-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-  
35 methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide

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5 NMR (DMSO-d<sub>6</sub>, δ) : 1.37-1.50 (2H, m), 1.50-1.63 (2H, m), 1.68-1.82 (2H, m), 2.14 (3H, s), 2.16-2.38 (9H, m), 2.93 (2H, t, J=5Hz), 3.14 (3H, s), 3.21 (3H, s), 3.36-3.47 (4H, m), 3.55 (2H, t, J=5Hz), 3.81-4.02 (2H, m), 6.63 (1H, d, J=8Hz), 6.76-6.87 (2H, m), 6.91 (1H, d, J=8Hz), 7.00 (1H, d, J=8Hz), 7.04-7.12 (2H, m), 7.88 (1H, d, J=8Hz), 7.95 (1H, d, J=8Hz)

10 Example 74

The following compound was obtained by using 4-[2-tert-butoxycarbonylamino-1H-benzimidazol-4-yl]carbamoxy-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)-carbonylpent-1-yloxy]phenyl]benzamide as a starting compound  
15 according to a similar manner to that of Example 23.

4-[2-Amino-1H-benzimidazol-4-yl]carbamoxy-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide

20 NMR (DMSO-d<sub>6</sub>, δ) : 1.37-1.50 (2H, m), 1.50-1.65 (2H, m), 1.65-1.82 (2H, m), 2.14 (3H, s), 2.17-2.38 (9H, m), 3.23 (3H, s), 3.36-3.48 (4H, m), 3.67-4.05 (5H, m), 6.20 (2H, br peak), 6.65 (1H, d, J=8Hz), 6.73-6.93 (3H, m), 6.96-7.14 (3H, m), 7.84-7.92 (2H, m)

25

Example 75

The following compounds were obtained according to a similar manner to that of Preparation 13.

30 1) 4-(2-Aminomethyl-1-methyl-1H-benzimidazol-4-yl)carbonylamino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide  
NMR (CDCl<sub>3</sub>, δ) : 1.44-1.75 (4H, m), 1.75-1.90 (2H, m), 2.25 (3H, s), 2.28 (3H, s), 2.30-2.41 (6H, m), 3.32  
35 (3H, s), 3.43-3.52 (2H, m), 3.57-3.66 (2H, m),

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3.74-3.90 (7H, m), 3.95 (1H, br peak), 4.20 (2H, s), 6.53-6.63 (2H, m), 6.87 (1H, d, J=8Hz), 6.98 (1H, d, J=8Hz), 7.03 (1H, s), 7.37 (1H, t, J=8Hz), 7.46 (1H, d, J=8Hz), 8.15 (1H, d, J=8Hz), 8.55 (1H, d, J=8Hz)

2) 4-(2-Aminomethyl-3-methyl-3H-benzimidazol-4-yl)carbonyl-amino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methyl-piperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide

10 NMR (CDCl<sub>3</sub>, δ) : 1.48-1.62 (2H, m), 1.62-1.93 (4H, m), 2.30 (3H, s), 2.32-2.41 (5H, m), 2.41-2.55 (4H, m), 3.33 (3H, s), 3.51-3.60 (2H, m), 3.60-3.77 (5H, m), 3.81 (3H, s), 3.87-4.03 (2H, m), 4.13 (2H, br peak), 6.61 (1H, d, J=8Hz), 6.65 (1H, s), 6.88 (1H, d, J=8Hz), 6.97 (1H, d, J=8Hz), 7.03 (1H, s), 7.22-7.30 (1H, m), 7.42 (1H, d, J=8Hz), 7.86 (1H, br peak), 8.30 (1H, d, J=8Hz), 8.35 (1H, s)

#### Example 76

20 A solution of 3-methoxy-N-methyl-N-(4-methyl-2-benzyloxyphenyl)-4-[2-(tert-butoxycarbonyl)aminomethyl-1H-benzimidazol-4-yl]carbonylaminobenzamide (260 mg) in 90% trifluoroacetic acid (2 ml) was stirred at ambient temperature for 2 hours and the solvent was evaporated in vacuo. The residue was stirred with chloroform (10 ml) and saturated aqueous sodium hydrogencarbonate (10 ml) and the organic phase was separated. The solution was washed with brine and dried over magnesium sulfate. The solvent was evaporated in vacuo and the residue was purified by NH type silica gel column (chloroform) to give 4-(2-aminomethyl-1H-benzimidazol-4-yl)carbonylamino-3-methoxy-N-methyl-N-(4-methyl-2-benzyloxyphenyl)benzamide (130 mg).

30 NMR (CDCl<sub>3</sub>, δ) : 2.22 (3H, s), 3.39 (3H, s), 3.57 (3H, s), 4.15 (2H, s), 4.88 (1H, d, J=12Hz), 5.04 (1H, d, J=12Hz), 6.60-6.70 (2H, m), 6.85-7.01 (3H, m),

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7.32 (1H, m), 7.38 (5H, s), 7.46 (1H, br s), 8.08  
(1H, br s), 8.47 (1H, br s)

Example 77

5       The following compounds were obtained according to a  
similar manner to that of Example 76.

- 1) 4-(2-Aminomethyl-1H-benzimidazol-4-yl)carbonylamino-N-  
(2,4-dimethylphenyl)-3-methoxy-N-methylbenzamide

10       NMR (DMSO-d<sub>6</sub>, δ) : 2.11 (3H, s), 2.19 (3H, s), 3.21  
(3H, s), 3.72 (3H, s), 4.08 (2H, s), 6.88-7.05 (4H,  
m), 7.14 (1H, d, J=8Hz), 7.31 (1H, t, J=8Hz), 7.71  
(1H, d, J=8Hz), 7.89 (1H, d, J=8Hz), 8.40 (1H, d,  
J=8Hz)

15

- 2) 4-(2-Aminomethyl-1H-benzimidazol-4-yl)carbonylamino-3-  
methoxy-N-(2-methoxy-4-methylphenyl)-N-methylbenzamide  
NMR (CDCl<sub>3</sub>, δ) : 2.25 (3H, s), 3.34 (3H, s), 3.67 (3H,  
s), 3.70 (3H, s), 4.15 (2H, s), 6.55-6.63 (2H, m),  
20       6.82-7.00 (3H, m), 7.26 (1H, t, J=8Hz), 7.48 (1H,  
br), 8.08 (1H, br), 8.52 (1H, br)

20

- 3) 4-(2-Aminomethyl-1H-benzimidazol-4-yl)carbonylamino-3-  
methoxy-N-methyl-N-[4-methyl-2-[4-(4-methylpiperazin-1-  
yl)carbonylphenylmethoxy]phenyl]benzamide

25

NMR (CDCl<sub>3</sub>, δ) : 2.26 (3H, s), 2.30 (3H, s), 2.31-2.50  
(4H, m), 3.40 (3H, s), 3.40-3.51 (2H, m), 3.62 (3H,  
s), 3.68-3.83 (2H, m), 4.17 (2H, s), 4.88 (1H, d,  
J=12Hz), 5.07 (1H, d, J=12Hz), 6.62 (1H, s), 6.70  
30       (1H, d, J=8Hz), 6.87-6.94 (2H, m), 7.03 (1H, d,  
J=8Hz), 7.20-7.44 (5H, m), 7.52 (1H, m), 7.99 (1H,  
br), 8.46 (1H, m)

30

- 4) 4-(2-Aminomethyl-1H-benzimidazol-4-yl)carbonylamino-3-  
methoxy-N-methyl-N-[4-methyl-2-[3-(4-methylpiperazin-1-

35

yl)carbonylprop-1-yloxy]phenyl]benzamide

NMR (CDCl<sub>3</sub>, δ) : 2.05-2.16 (2H, m), 2.23 (3H, s), 2.30-2.41 (4H, m), 2.52 (2H, t, J=7.5Hz), 3.33 (3H, s), 3.43-3.50 (2H, m), 3.59-3.65 (2H, m), 3.75 (3H, s), 3.86-4.06 (2H, m), 4.21 (2H, s), 6.58-6.67 (2H, m), 6.90-7.02 (3H, m), 7.28 (1H, t, J=8Hz), 7.56 (1H, br), 8.06 (1H, br), 8.49 (1H, br)

5) 4-(2-Aminomethyl-1H-benzimidazol-4-yl)carbonylamino-3-methoxy-N-methyl-N-[4-methyl-2-[4-(4-methylpiperazin-1-yl)carbonylbut-1-yloxy]phenyl]benzamide

NMR (CDCl<sub>3</sub>, δ) : 1.76-1.93 (4H, m), 2.25 (3H, s), 2.28 (3H, s), 2.31-2.47 (4H, m), 3.33 (3H, s), 3.49 (1H, m), 3.60-3.74 (5H, m), 3.86 (1H, m), 3.96 (1H, m), 4.17 (2H, s), 6.59-6.65 (2H, m), 6.86-6.95 (2H, m), 7.00 (1H, d, J=8Hz), 7.21 (1H, t, J=8Hz), 7.39 (1H, m), 8.02 (1H, m), 8.50 (1H, m)

6) 4-(2-Aminomethyl-1H-benzimidazol-4-yl)carbonylamino-3-methoxy-N-methyl-N-[4-methyl-2-(5-piperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide

NMR (DMSO-d<sub>6</sub>, δ) : 1.39-1.52 (2H, m), 1.52-1.63 (2H, m), 1.70-1.81 (2H, m), 2.22 (3H, s), 2.37 (2H, t, J=7.5Hz), 2.98-3.13 (4H, m), 3.20 (3H, s), 3.61-3.71 (4H, m), 3.77 (3H, s), 3.88 (1H, m), 3.97 (1H, m), 4.42 (2H, s), 6.66 (1H, d, J=8Hz), 6.83 (1H, s), 6.92-6.99 (2H, m), 7.05 (1H, d, J=8Hz), 7.41 (1H, t, J=8Hz), 7.83 (1H, d, J=8Hz), 7.97 (1H, d, J=8Hz), 8.35 (1H, br)

7) 4-(2-Aminomethyl-1H-benzimidazol-4-yl)carbonylamino-N-[2-(5-carbamoylpent-1-yloxy)-4-methylphenyl]-3-methoxy-N-methylbenzamide

NMR (CDCl<sub>3</sub>, δ) : 1.46-1.57 (2H, m), 1.66-1.82 (4H, m), 2.20-2.30 (2H, m), 2.23 (3H, s), 3.32 (3H, s), 3.61

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(3H, s), 3.76 (1H, m), 3.91 (1H, m), 4.12 (2H, s),  
5.93 (1H, br), 6.32 (1H, br), 6.54-6.63 (2H, m),  
6.73 (1H, s), 6.93 (1H, d, J=8Hz), 7.01 (1H, d,  
J=8Hz), 7.18 (1H, t, J=8Hz), 7.43 (1H, m), 7.90  
(1H, m), 8.46 (1H, d, J=8Hz)

5

- 8) 4-(2-Aminomethyl-1H-benzimidazol-4-yl)carbonylamino-N-  
[2-(5-dimethylcarbamoylpent-1-yloxy)-4-methylphenyl]-3-  
methoxy-N-methylbenzamide

10 NMR (DMSO-d<sub>6</sub>, δ) : 1.48-1.60 (2H, m), 1.66-1.77 (2H,  
m), 1.77-1.90 (2H, m), 2.28 (3H, s), 2.38 (2H, t,  
J=7.5Hz), 2.93 (3H, s), 3.00 (3H, s), 3.35 (3H, s),  
3.72 (3H, s), 3.85 (1H, m), 3.96 (1H, m), 4.17 (2H,  
s), 6.55-6.63 (2H, m), 6.86 (1H, d, J=8Hz), 6.91  
15 (1H, s), 6.97 (1H, d, J=8Hz), 7.24 (1H, t, J=8Hz),  
7.49 (1H, br), 8.05 (1H, br), 8.50 (1H, br)

- 9) 4-(2-Aminomethyl-1H-benzimidazol-4-yl)carbonylamino-N-  
[2-[5-(2,2-dimethylhydrazino)carbonylpent-1-yloxy]-4-  
methylphenyl]-3-methoxy-N-methylcarbonylaminobenzamide

20 NMR (CDCl<sub>3</sub>, δ) : 1.42-1.62 (2H, m), 1.62-1.90 (4H, m),  
2.12 (2H, t, J=7.5Hz), 2.27 (3H, s), 2.50 (3H, s),  
2.58 (3H, s), 3.34 (3H, s), 3.71 (3H, s), 3.77-4.00  
(2H, m), 4.20 (2H, s), 6.27 (1H, br), 6.52-6.67  
25 (2H, m), 6.83-7.11 (3H, m), 7.24 (1H, m), 7.50 (1H,  
br), 8.07 (1H, br), 8.53 (1H, br)

- 10) 4-(2-Aminomethyl-1H-benzimidazol-4-yl)carbonylamino-3-  
methoxy-N-methyl-N-[4-methyl-2-[5-(4-oxopiperidin-1-  
yl)carbonylpent-1-yloxy]phenyl]benzamide

30 NMR (CDCl<sub>3</sub>, δ) : 1.41-1.60 (2H, m), 1.60-1.89 (4H, m),  
2.21 (3H, s), 2.30-2.50 (6H, m), 3.30 (3H, s),  
3.41-3.98 (6H, m), 4.22 (2H, s), 6.51-6.62 (2H, m),  
6.78-6.99 (3H, m), 7.24 (1H, m), 7.55 (1H, br),  
35 7.96 (1H, br), 8.45 (1H, br)

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11) 4-(2-Aminomethyl-1H-benzimidazol-4-yl)carbonylamino-N-[2-[5-(4-hydroxypiperidin-1-yl)carbonylpent-1-yloxy]-4-methylphenyl]-3-methoxy-N-methylbenzamide

5 NMR (CDCl<sub>3</sub>, δ) : 1.35-1.54 (4H, m), 1.54-1.72 (2H, m),  
1.72-1.91 (4H, m), 2.24 (3H, s), 2.28-2.41 (2H, m),  
2.95-3.21 (2H, m), 3.30 (3H, s), 3.46-3.98 (4H, m),  
3.70 (3H, s), 4.09 (1H, m), 4.20 (2H, s), 6.52-6.63  
(2H, m), 6.78-6.97 (3H, m), 7.13 (1H, m), 7.41 (1H,  
br), 7.88 (1H, br), 8.38 (1H, d, J=8Hz)

10

12) 4-(2-Aminomethyl-1H-benzimidazol-4-yl)carbonylamino-N-[2-[5-[N-(2-dimethylaminoeth-1-yl)-N-methylamino-carbonyl]pent-1-yloxy]-4-methylphenyl]-3-methoxy-N-methylbenzamide

15 NMR (CDCl<sub>3</sub>, δ) : 1.31-1.52 (2H, m), 1.59-1.81 (4H, m),  
2.23 (3H, s), 2.30-2.41 (2H, m), 2.73-2.88 (2H, m),  
2.85 (6H, sx2), 3.05 (3H, s), 3.29 (1H, s), 3.55-  
3.94 (4H, m), 4.46 (2H, m), 6.52-6.63 (2H, m), 6.67  
(1H, s), 6.82-7.10 (3H, m), 7.31 (1H, m), 7.75 (1H,  
20 m), 8.33 (1H, m)

20

#### Example 78

The following compound was obtained according to similar manners to those of Examples 38 and 76.

25

4-(2-Aminomethyl-1H-benzimidazol-4-yl)carbonylamino-N-[2-(6-hydroxyhex-1-yl)oxy-4-methyl]phenyl-3-methoxy-N-methylbenzamide dihydrochloride

30 NMR (DMSO-d<sub>6</sub>, δ) : 1.31-1.50 (4H, m), 1.67-1.76 (2H,  
m), 2.21 (3H, s), 3.18 (3H, s), 3.40 (2H, t,  
J=7.5Hz), 3.74 (3H, s), 3.74-3.85 (2H, m), 3.85  
(1H, m), 3.97 (1H, m), 4.45 (1H, m), 4.79 (2H, m),  
6.64 (1H, d, J=8Hz), 6.81 (1H, s), 7.90 (1H, d,  
J=8Hz), 6.97 (1H, s), 7.03 (1H, d, J=8Hz), 7.39  
35 (1H, t, J=8Hz), 7.77 (1H, d, J=8Hz), 7.94 (1H, d,

J=8Hz), 8.34 (1H, d, J=8Hz), 8.71 (1H, br)

#### Example 79

To the solution of 3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]-4-[2-(3-phthalimidopropyl)-1H-benzimidazol-4-yl]carbonylamino benzamide (160 mg) in ethanol (5 ml) was added hydrazine hydrate (49 mg) and stirred at ambient temperature for 6 hours. After the reaction mixture was concentrated in vacuo, the residue was purified by preparative thin-layer chromatography (methanol:chloroform:28% ammonia solution = 3:5:1). To the purified product was added water and 1N hydrochloric acid (0.5l ml). The solution was lyophilized to give 4-[2-(3-aminopropyl)-1H-benzimidazol-4-yl]carbonylamino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide trihydrochloride (70 mg).

NMR (DMSO-d<sub>6</sub>, δ) : 1.42-1.50 (2H, m), 1.50-1.63 (2H, m), 1.70-1.82 (2H, m), 2.12-2.22 (2H, m), 2.22 (3H, s), 2.40 (2H, t, J=7Hz), 2.73 (3H, s), 2.80-3.17 (6H, m), 3.20 (3H, s), 3.33-3.57 (4H, m), 3.72 (3H, s), 3.87-4.10 (3H, m), 4.40-4.47 (1H, m), 6.63 (1H, d, J=8Hz), 6.82 (1H, s), 6.90-6.93 (2H, m), 7.04 (1H, d, J=8Hz), 7.43 (1H, t, J=8Hz), 7.82 (1H, d, J=8Hz), 7.97-8.13 (2H, m), 8.21 (2H, br s)

#### Example 80

The solution of 4-[(1-tert-butoxycarbonyl-2-tert-butyl)diphenylsilyloxymethylindol-4-yl]carbonylamino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide (615 mg) in 1N sodium hydroxide aqueous solution (3.1 ml) and methanol (10 ml) was stirred at ambient temperature overnight. The resulting solution was neutralized with 1N hydrochloric acid and extracted with ethyl acetate (20 ml). The organic layer was washed with brine, dried over magnesium sulfate and



concentrated in vacuo. The residue was purified by silica gel column chromatography (eluent; 8-10% methanol in chloroform) to give 4-[(2-hydroxymethylindol-4-yl)carbonyl]-amino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide (362 mg).

NMR (CDCl<sub>3</sub>, δ) : 1.44-1.57 (2H, m), 1.63-1.85 (4H, m), 2.27 (3H, s), 2.29 (3H, s), 2.30-2.40 (6H, m), 3.33 (3H, s), 3.43-3.50 (2H, m), 3.57-3.63 (2H, m), 3.70 (3H, s), 3.82-3.99 (2H, m), 4.80 (2H, s), 6.59-6.67 (2H, m), 6.77 (1H, s), 6.89 (1H, d, J=8Hz), 6.95 (1H, d, J=8Hz), 6.98 (1H, s), 7.18 (1H, t, J=8Hz), 7.42 (1H, d, J=8Hz), 7.57 (1H, d, J=8Hz), 8.32 (1H, d, J=8Hz), 8.64 (1H, s), 8.98-9.03 (1H, br s)

#### Example 81

The following compound was obtained by using 4-[(1-tert-butoxycarbonyl-2-benzyloxymethylindolin-4-yl)carbonyl]amino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide as a starting compound according to a similar manner to that of Preparation 10.

4-[(1-tert-Butoxycarbonyl-2-hydroxymethylindolin-4-yl)carbonyl]amino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide

NMR (DMSO-d<sub>6</sub>, δ) : 1.40-1.61 (4H, m), 1.50 (9H, s), 1.69-1.79 (2H, s), 2.23 (3H, s), 2.35-2.42 (2H, m), 2.69 (3H, s), 2.98-3.22 (9H, m), 3.28-3.54 (5H, m), 3.64 (3H, s), 3.84-4.00 (2H, m), 4.10-4.18 (1H, br), 4.31-4.40 (1H, m), 4.89 (1H, t, J=5Hz), 6.65 (1H, d, J=8Hz), 6.82 (1H, s), 6.88-6.92 (2H, m), 7.03 (1H, d, J=8Hz), 7.20-7.33 (2H, m), 7.76 (1H, d, J=8Hz), 9.13 (1H, s)

#### Example 82

To an ice bath cooled solution of 4-(2-aminomethyl-1H-

benzimidazol-4-yl)carbonylamino-N-[2-(5-ethoxycarbonylpent-1-yloxy)-4-methylphenyl]-3-methoxy-N-methylbenzamide (2.95 g) in dichloromethane (30 ml) were added triethylamine (496 mg) and di-tert-butyl dicarbonate (1.07 g) and the mixture was stirred at ambient temperature for 3 hours. The solution was washed successively with water, 10% hydrochloric acid, saturated aqueous sodium hydrogencarbonate and brine and the organic phase was dried over magnesium sulfate. The solvent was evaporated in vacuo and the residue was purified by silica gel column (1% methanol in chloroform) to give N-[2-(5-ethoxycarbonylpent-1-yloxy)-4-methylphenyl]-3-methoxy-N-methyl-4-[2-(tert-butoxycarbonylamino)methyl-1H-benzimidazol-4-yl]carbonylaminobenzamide (2.65 g).

NMR (CDCl<sub>3</sub>, δ) : 1.24 (3H, t, J=7.5Hz), 1.41-1.55 (2H, m), 1.48 (9H, s), 1.63-1.84 (4H, m), 2.23 (3H, s), 2.31 (2H, t, J=7.5Hz), 3.32 (3H, s), 3.78 (3H, s), 3.78-3.98 (2H, m), 4.12 (2H, q, J=7.5Hz), 4.58 (2H, m), 5.68 (1H, br t, J=7Hz), 6.53-6.63 (2H, m), 6.83-7.04 (3H, m), 7.30 (1H, t, J=8Hz), 7.50 (1H, d, J=8Hz), 8.11 (1H, d, J=8Hz), 8.49 (1H, d, J=8Hz)

### Example 83

The solution of 4-[(2-ethoxycarbonylindolin-4-yl)-carbonyl]amino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide (175 mg) in ammonia-methanol solution (8.0 ml) was stood overnight at ambient temperature. The solvent was evaporated in vacuo and the residue was purified by silica gel column chromatography (eluent; 8-10% methanol in chloroform) to give 4-[(2-carbamoylindolin-4-yl)carbonyl]amino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide (160 mg).

NMR (CDCl<sub>3</sub>, δ) : 1.48-1.58 (2H, m), 1.64-1.87 (4H, m), 2.28 (3H, s), 2.30 (3H, s), 2.32-2.41 (6H, m), 3.32 (3H, s), 3.46-3.51 (2H, m), 3.59-3.65 (2H, m), 3.77

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(3H, s), 3.84-3.98 (3H, m), 4.38-4.49 (2H, m),  
5.46-5.50 (1H, br s), 6.59 (1H, d, J=8Hz), 6.62  
(1H, s), 6.69-6.74 (1H, br), 6.85 (1H, d,  
J=8Hz), 6.91 (1H, d, J=8Hz), 7.01 (1H, s), 7.09 (1H,  
5 d, J=8Hz), 7.18 (1H, t, J=8Hz), 8.22 (1H, d,  
J=8Hz), 8.37 (1H, s)

#### Example 84

To a solution of 4-[(2-hydroxymethylindol-4-yl)-  
10 carbonyl]amino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-  
methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide  
(295 mg) in dichloromethane (8.0 ml) was added manganese(IV)  
oxide (196 mg) and the mixture was stirred at ambient  
temperature for 3 hours. The resulting mixture was filtered  
15 through a bed of celite and the filtrate was concentrated in  
vacuo. The residue was triturated with diethyl ether-n-  
hexane (1:3) to give 4-[(2-formylindol-4-yl)carbonyl]amino-3-  
methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-  
yl)carbonylpent-1-yloxy]phenyl]benzamide (255 mg).

20 NMR (CDCl<sub>3</sub>, δ) : 1.49-1.61 (2H, m), 1.68-1.89 (4H, m),  
2.28 (3H, s), 2.29 (3H, s), 2.31-2.43 (6H, m), 3.36  
(3H, s), 3.47-3.52 (2H, m), 3.60-3.68 (2H, m), 3.78  
(3H, s), 3.86-4.00 (2H, m), 6.60 (1H, d, J=8Hz),  
6.65 (1H, s), 6.88 (1H, d, J=8Hz), 6.98 (1H, d,  
25 J=8Hz), 7.07 (1H, s), 7.46 (1H, t, J=8Hz), 7.58  
(1H, d, J=8Hz), 7.62 (1H, d, J=8Hz), 7.84 (1H, s),  
8.35 (1H, d, J=8Hz), 8.62 (1H, s), 9.44-9.50 (1H,  
br s), 9.89 (1H, s)

#### Example 85

A solution of 4-(2-aminomethyl-1H-benzimidazol-4-  
yl)carbonylamino-3-methoxy-N-methyl-N-(2-benzyloxy-4-  
methylphenyl)benzamide (120 mg) in methanol (15 ml) was  
stirred under atmospheric pressure of hydrogen in the presence  
35 of palladium hydroxide (20 mg) at ambient temperature

overnight. After removal of the catalyst by filtration, the filtrate was evaporated in vacuo to give 4-(2-aminomethyl-1H-benzimidazol-4-yl)carbonylamino-3-methoxy-N-methyl-N-(2-hydroxy-4-methylphenyl)benzamide (85 mg).

5       NMR (DMSO- $d_6$ ,  $\delta$ ) : 2.13 (3H, s), 3.19 (3H, s), 3.77  
                                  (3H, s), 4.63 (2H, m), 6.47 (1H, d, J=8Hz), 6.69  
                                  (1H, s), 6.86 (1H, d, J=8Hz), 6.97 (1H, d, J=8Hz),  
                                  7.03 (1H, s), 7.42 (1H, t, J=8Hz), 7.83 (1H, d,  
                                  J=8Hz), 7.98 (1H, d, J=8Hz), 8.30 (1H, br), 8.78  
10                               (2H, br)

#### Example 86

The following compound was obtained by using 4-(2-amino-3-nitrophenyl)carbonylamino-N-[2-(4-methoxybenzyloxy)-4-methylphenyl]-3-methoxy-N-methylbenzamide as a starting  
15       compound according to a similar manner to that of Example 85.

4-(2-Amino-3-nitrophenyl)carbonylamino-N-(2-hydroxy-4-methylphenyl)-3-methoxy-N-methylbenzamide

20       NMR (CDCl<sub>3</sub>,  $\delta$ ) : 2.23 (3H, s), 3.37 (3H, s), 3.67 (3H,  
                                  s), 6.48-7.02 (7H, m), 7.63 (1H, d, J=8Hz), 8.03-  
                                  8.13 (3H, m), 8.21-8.30 (2H, m)

#### Example 87

25       The following compound was obtained by using N-[2-(5-ethoxycarbonylpent-1-yloxy)-4-methylphenyl]-3-methoxy-N-methyl-4-[2-(tert-butoxycarbonylamino)methyl-1H-benzimidazol-4-yl]carbonylamino benzamide as a starting compound according to a similar manner to that of Example 29.

30

N-[2-(5-Carboxypent-1-yloxy)-4-methylphenyl]-3-methoxy-N-methyl-4-[2-(tert-butoxycarbonylamino)methyl-1H-benzimidazol-4-yl]carbonylamino benzamide

35       NMR (CDCl<sub>3</sub>,  $\delta$ ) : 1.50 (9H, s), 1.50-1.63 (2H, m), 1.69-  
                                  1.85 (4H, m), 2.24 (3H, s), 2.36-2.50 (2H, m), 3.33

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(3H, s), 3.63 (3H, s), 3.80 (1H, m), 3.95 (1H, m),  
4.54 (2H, m), 6.09 (1H, br), 6.52-6.63 (2H, m),  
6.78-7.01 (3H, m), 7.22 (1H, t, J=8Hz), 7.48 (1H,  
m), 7.90 (1H, m), 8.39 (1H, m)

5

Example 88

A mixture of N-[2-(5-carboxypent-1-yloxy)-4-methyl-  
phenyl]-3-methoxy-N-methyl-4-[2-(tert-butoxycarbonylamino)-  
methyl-1H-benzimidazol-4-yl]carbonylaminobenzamide (200 mg),  
10 4-(tert-butoxycarbonyl)piperazine (66.3 mg), 1-(3-dimethyl-  
aminopropyl)-3-ethylcarbodiimide hydrochloride (68.3 mg) and  
1-hydroxybenzotriazol (48.1 mg) in N,N-dimethylformamide (5  
ml) was stirred at ambient temperature overnight and the  
mixture was diluted with ethyl acetate. The solution was  
15 washed successively with saturated aqueous sodium hydrogen  
carbonate solution, water and brine and dried over magnesium  
sulfate. The solvent was evaporated and the residue was  
purified by silica gel column (chloroform) to give 3-methoxy-  
N-methyl-N-[4-methyl-2-[5-(4-tert-butoxycarbonylpiperazin-1-  
20 yl)carbonylpent-1-yloxy]phenyl]-4-[2-(tert-butoxycarbonyl)-  
aminomethyl-1H-benzimidazol-4-yl]carbonylaminobenzamide (250  
mg).

NMR (CDCl<sub>3</sub>, δ) : 1.45-1.56 (2H, m), 1.45 (9H, s), 1.50  
(9H, s), 1.62-1.87 (4H, m), 2.26 (3H, s), 2.35 (2H,  
25 t, J=7.5Hz), 3.32 (3H, s), 3.35-3.47 (6H, m), 3.51-  
3.60 (2H, m), 3.77-3.99 (2H, m), 3.82 (3H, s), 4.37  
(2H, m), 5.74 (1H, br), 6.55-6.62 (2H, m), 6.84-  
7.03 (3H, m), 7.31 (1H, t, J=8Hz), 7.51 (1H, d,  
J=8Hz), 8.12 (1H, d, J=8Hz), 8.50 (1H, d, J=8Hz)

30

Example 89

The following compounds were obtained according to a  
similar manner to that of Example 88.

35 1) 3-Methoxy-N-methyl-N-[4-methyl-2-[5-(4-oxopiperidin-1-

yl)carbonylpent-1-yloxy]phenyl]-4-[2-(tert-butoxy-carbonyl)aminomethyl-1H-benzimidazol-4-yl]-carbonylaminobenzamide

5 NMR (CDCl<sub>3</sub>, δ) : 1.47-1.60 (2H, m), 1.47 (9H, s), 1.70-1.88 (4H, m), 2.23 (3H, s), 2.37-2.57 (2H, m), 3.33 (3H, s), 3.69-3.99 (4H, m), 3.80 (3H, s), 4.60 (2H, d, J=7Hz), 5.75 (1H, br), 6.55-6.66 (2H, m), 6.85-7.01 (3H, m), 7.31 (1H, t, J=8Hz), 7.59 (1H, d, J=8Hz), 8.00 (1H, d, J=8Hz), 8.46 (1H, d, J=8Hz)

10

2) N-[2-(5-Carbamoylpent-1-yloxy)-4-methylphenyl]-3-methoxy-N-methyl-4-[2-(tert-butoxycarbonylamino)methyl-1H-benzimidazol-4-yl]carbonylaminobenzamide

15 NMR (CDCl<sub>3</sub>, δ) : 1.50 (9H, s), 1.60-1.86 (6H, m), 2.21-2.30 (2H, m), 2.26 (3H, s), 3.33 (3H, s), 3.70 (3H, s), 3.72-3.97 (2H, m), 4.56 (2H, m), 6.57-6.68 (2H, m), 6.93-7.05 (3H, m), 7.33 (1H, m), 7.54 (1H, m), 8.01 (1H, s), 8.11 (1H, d, J=8Hz), 8.50 (1H, m)

20

3) N-[2-(5-Dimethylcarbamoylpent-1-yloxy)-4-methylphenyl]-3-methoxy-N-methyl-4-[2-(tert-butoxycarbonylamino)methyl-1H-benzimidazol-4-yl]carbonylaminobenzamide

25 NMR (CDCl<sub>3</sub>, δ) : 1.45-1.57 (2H, m), 1.49 (9H, s), 1.64-1.85 (4H, m), 2.27 (3H, s), 2.35 (2H, t, J=7.5Hz), 2.92 (3H, s), 3.00 (3H, s), 3.34 (3H, s), 3.79 (3H, s), 3.84 (1H, m), 3.94 (1H, m), 4.58 (2H, d, J=7Hz), 5.72 (1H, br), 6.55-6.64 (2H, m), 6.90 (1H, d, J=8Hz), 6.92-7.01 (2H, m), 7.28 (1H, t, J=8Hz), 7.48 (1H, d, J=8Hz), 8.02 (1H, s), 8.10 (1H, d, J=8Hz), 8.50 (1H, d, J=8Hz)

30

4) N-[2-[5-(2,2-Dimethylhydrazino)carbonylpent-1-yloxy]-4-methylphenyl]-3-methoxy-N-methyl-4-[2-(tert-butoxycarbonylamino)methyl-1H-benzimidazol-4-yl]-carbonylaminobenzamide

35

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NMR (CDCl<sub>3</sub>,  $\delta$ ) : 1.41-1.58 (2H, m), 1.50 (9H, s), 1.63-1.89 (4H, m), 2.13 (2H, t, J=7.5Hz), 2.27 (3H, s), 2.50 (3H, s), 2.58 (3H, s), 3.35 (3H, s), 3.72-4.01 (2H, m), 3.79 (3H, s), 4.58 (2H, m), 5.81 (1H, br),  
5 6.52-6.67 (2H, m), 6.84-7.05 (3H, m), 7.30 (1H, t, J=8Hz), 7.49 (1H, m), 8.11 (1H, m), 8.51 (1H, m)

5) N-[2-[5-[N-(2-Dimethylaminoeth-1-yl)-N-methylamino-carbonyl]pent-1-yloxy]-4-methylphenyl]-3-methoxy-N-methyl-4-[2-(tert-butoxycarbonyl)aminomethyl-1H-benzimidazol-4-yl]carbonylamino benzamide

10 NMR (CDCl<sub>3</sub>,  $\delta$ ) : 1.41-1.56 (2H, m), 1.48 (9H, s), 1.61-1.74 (2H, m), 1.74-1.85 (2H, m), 2.24 (3H, s), 2.32 (6H, s), 2.32-2.44 (2H, m), 2.53 (2H, t, J=7.5Hz),  
15 3.32 (3H, s), 3.52 (2H, t, J=7.5Hz), 3.78 (3H, s), 3.86 (1H, m), 3.96 (1H, m), 4.58 (2H, m), 5.92 (1H, br), 6.53-6.61 (2H, m), 6.87 (1H, d, J=8Hz), 6.91-7.02 (2H, m), 7.29 (1H, t, J=8Hz), 7.50 (1H, m),  
20 8.11 (1H, d, J=8Hz), 8.49 (1H, m)

#### Example 90

The following compound was obtained by using 4-(1H-benzimidazol-4-yl)carbonylamino-N-(2-carboxy-4-methylphenyl)-3-methoxy-N-methylbenzamide as a starting compound according  
25 to a similar manner to that of Example 88.

4-(1H-Benzimidazol-4-yl)carbonylamino-N-(2-carbamoyl-4-methylphenyl)-3-methoxy-N-methylbenzamide

30 NMR (CDCl<sub>3</sub>,  $\delta$ ) : 2.29 (3H, s), 3.45 (3H, s), 3.71 (3H, s), 6.93 (1H, d, J=8Hz), 7.00-7.10 (2H, m), 7.14-7.43 (3H, m), 7.67 (1H, d, J=8Hz), 7.93 (1H, d, J=8Hz), 8.09 (1H, s), 8.31 (1H, d, J=8Hz)

#### Example 91

35 The following compound was obtained according to a

similar manner to that of Example 90.

N-(2-Dimethylcarbamoyl-4-methylphenyl)-3-methoxy-N-methyl-4-(2-methyl-1H-benzimidazol-4-yl)carbonylamino-  
5 benzamide

NMR (CDCl<sub>3</sub>, δ) : 2.31 (3H, s), 2.56 (3H, s), 2.99 (6H, s), 3.42 (3H, s), 3.76 (3H, s), 6.89-7.32 (6H, m), 7.44 (1H, d, J=8Hz), 8.08 (1H, d, J=8Hz), 8.59 (1H, br)

#### Example 92

To a solution of 3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-oxopiperidin-1-yl)carbonylpent-1-yloxy]phenyl]-4-[2-(tert-butoxycarbonyl)aminomethyl-1H-benzimidazol-4-yl]-  
15 carbonylamino benzamide (150 mg) in methanol (5 ml) was added sodium borohydride (7.52 mg) under an ice bath cooling and the mixture was stirred at the same temperature for 1 hour. The mixture was diluted with chloroform and the solution was washed with water and brine. The organic phase was dried  
20 over magnesium sulfate and the solvent was evaporated in vacuo to give N-[2-[5-(4-hydroxypiperidin-1-yl)carbonylpent-1-yloxy]-4-methylphenyl]-3-methoxy-N-methyl-4-[2-(tert-butoxycarbonyl)aminomethyl-1H-benzimidazol-4-yl]carbonylamino benzamide (150 mg).

25 NMR (CDCl<sub>3</sub>, δ) : 1.48 (9H, s), 1.48-1.57 (2H, m), 1.64-1.94 (8H, m), 2.27 (3H, s), 2.30-2.41 (2H, m), 3.03-3.23 (2H, m), 3.33 (3H, s), 3.79 (3H, s), 3.80-3.97 (4H, m), 4.12 (1H, m), 4.61 (2H, d, J=7Hz), 5.86 (1H, br), 6.54-6.63 (2H, m), 6.84-7.00  
30 (3H, m), 7.32 (1H, t, J=8Hz), 7.59 (1H, d, J=8Hz), 7.98 (1H, br), 8.43 (1H, d, J=8Hz)

#### Example 93

A mixture of 4-(2-amino-3-nitrophenyl)carbonylamino-N-(2-hydroxy-4-methylphenyl)-3-methoxy-N-methylbenzamide (400



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mg), acetic anhydride (90.7 mg) and triethylamine (89.9 mg) in dichloromethane (20 ml) was stirred in an ice bath for 4 hours. The mixture was diluted with chloroform and the solution was washed with water and brine. The organic phase was dried over magnesium sulfate and the solvent was evaporated in vacuo to give N-(2-acetoxy-4-methylphenyl)-4-(2-amino-3-nitrophenyl)carbonylamino-3-methoxy-N-methylbenzamide (425 mg).

NMR (CDCl<sub>3</sub>, δ) : 2.21 (3H, s), 2.30 (3H, s), 3.35 (3H, s), 3.72 (3H, s), 6.68 (1H, t, J=8Hz), 6.88 (1H, s), 6.92-7.01 (2H, m), 7.10 (1H, d, J=8Hz), 7.70 (1H, d, J=8Hz), 8.14 (2H, br), 8.23 (1H, d, J=8Hz), 8.22 (1H, d, J=8Hz), 8.36 (1H, br)

#### Example 94

A mixture of 4-(2-amino-3-nitrophenyl)carbonylamino-N-(2-hydroxy-4-methylphenyl)-3-methoxy-N-methylbenzamide (520 mg), N-(4-bromobutyl)phthalimide (326 mg) and potassium carbonate (160 mg) in N,N-dimethylformamide (10 ml) was heated at 60°C for 8 hours. The mixture was diluted with ethyl acetate and the solution was washed with water and brine. The organic phase was dried over magnesium sulfate and the solvent was evaporated in vacuo. The crude oil was purified by silica gel column (1% methanol in chloroform) to give 4-(2-amino-3-nitrophenyl)carbonylamino-3-methoxy-N-methyl-N-[2-(4-phthalimidobut-1-yloxy)-4-methylphenyl]-benzamide (670 mg).

NMR (CDCl<sub>3</sub>, δ) : 1.78-1.96 (4H, m), 2.27 (3H, s), 3.31 (3H, s), 3.68-3.80 (5H, m), 3.92 (1H, m), 4.00 (1H, m), 6.57-6.72 (3H, m), 6.81-7.08 (3H, m), 7.66-7.73 (2H, m), 7.81-7.88 (2H, m), 8.09-8.21 (2H, m), 8.32 (1H, m)

#### Example 95

The following compound was obtained by using N-[2-(4-

phthalimidobut-1-yloxy)-4-methylphenyl]-3-methoxy-N-methyl-4-(2-methyl-1H-benzimidazol-4-yl)carbonylaminobenzamide as a starting compound according to a similar manner to that of Example 26.

5

N-[2-(4-Aminobut-1-yloxy)-4-methylphenyl]-3-methoxy-N-methyl-4-(2-methyl-1H-benzimidazol-4-yl)carbonylamino-benzamide

10 NMR (CDCl<sub>3</sub>, δ) : 1.53-1.70 (2H, m), 1.75-1.86 (2H, m),  
2.23 (3H, s), 2.57 (3H, s), 2.77 (2H, t, J=7.5Hz),  
3.34 (3H, s), 3.66 (3H, s), 3.80 (1H, m), 3.92 (1H,  
m), 6.54-6.61 (2H, m), 6.81-6.92 (2H, m), 6.98 (1H,  
d, J=8Hz), 7.21 (1H, t, J=8Hz), 7.51 (1H, br), 7.94  
15 (1H, br), 8.45 (1H, br)

15

#### Example 96

The following compound was obtained according to a similar manner to that of Example 95.

20

N-[2-(6-Aminohex-1-yl)oxy-4-methyl]phenyl-3-methoxy-N-methyl-4-[2-(tert-butoxycarbonyl)aminomethyl-1H-benzimidazol-4-yl]carbonylaminobenzamide

25 NMR (CDCl<sub>3</sub>, δ) : 1.33-1.50 (4H, m), 1.48 (9H, s), 1.52-  
1.63 (2H, m), 1.68-1.80 (2H, m), 2.25 (3H, s), 2.79  
(2H, t, J=7.5Hz), 3.32 (3H, s), 3.72 (3H, s), 3.78  
(1H, m), 3.90 (1H, m), 4.52 (2H, m), 6.02 (1H, br),  
6.51-6.62 (2H, m), 6.86-7.00 (3H, m), 7.20 (1H, t,  
J=8Hz), 7.48 (1H, d, J=8Hz), 7.91 (1H, d, J=8Hz),  
8.32 (1H, d, J=8Hz)

30

#### Example 97

The following compound was obtained by using N-[2-(5-tert-butoxycarbonylaminopent-1-yl)oxy-4-methyl]phenyl-3-methoxy-N-methyl-4-(2-methyl-1H-benzimidazol-4-yl)-  
35 carbonylaminobenzamide as a starting compound according to a

similar manner to that of Example 23.

N-[2-(5-Aminopent-1-yl)oxy-4-methyl]phenyl-3-methoxy-N-methyl-4-(2-methyl-1H-benzimidazol-4-yl)carbonylamino-  
5 benzamide

NMR (CDCl<sub>3</sub>, δ) : 1.40-1.53 (2H, m), 1.53-1.64 (2H, m),  
1.71-1.80 (2H, m), 2.25 (3H, s), 2.59 (3H, s), 2.78  
(2H, t, J=7.5Hz), 3.35 (3H, s), 3.68 (3H, s), 3.76  
(1H, m), 3.92 (1H, m), 6.51-6.62 (2H, m), 6.83 (1H,  
10 s), 6.91 (1H, d, J=8Hz), 7.00 (1H, d, J=8Hz), 7.22  
(1H, t, J=8Hz), 7.52 (1H, d, J=8Hz), 7.90 (1H, br),  
8.41 (1H, d, J=8Hz)

#### Example 98

15 The following compound was obtained according to a  
similar manner to that of Example 97.

N-[2-(4-Aminobut-1-yl)oxy-4-methyl]phenyl-3-methoxy-N-methyl-4-(2-methyl-1H-benzimidazol-4-yl)carbonylbenzamide

20 MASS (m/z) : 516

#### Example 99

To a solution of N-[2-(4-aminobut-1-yloxy)-4-methylphenyl]-3-methoxy-N-methyl-4-(2-methyl-1H-benzimidazol-4-yl)carbonylaminobenzamide (120 mg) in dichloromethane (10  
25 ml) was added acetic anhydride (23.8 mg) and the mixture was  
stirred at ambient temperature for 1 hour. The solution was  
washed with water and brine and dried over magnesium sulfate  
and the solvent was evaporated in vacuo. The residue was  
30 purified by silica gel column (2% methanol in chloroform) and  
the product was solidified with diethyl ether to give N-[2-(4-acetylaminobut-1-yloxy)-4-methylphenyl]-3-methoxy-N-methyl-4-(2-methyl-1H-benzimidazol-4-yl)-  
carbonylaminobenzamide (87 mg).

35 NMR (CDCl<sub>3</sub>, δ) : 1.58-1.86 (2H, m), 2.08 (3H, s), 2.26

230

(3H, s), 2.69 (3H, s), 3.19-3.41 (2H, m), 3.35 (3H, s), 3.73-3.87 (2H, m), 3.76 (3H, s), 6.23 (1H, br), 6.51-6.78 (3H, m), 6.90-7.10 (3H, m), 7.27 (1H, m), 7.59 (1H, d, J=8Hz), 7.91 (1H, d, J=8Hz), 8.45 (1H, d, J=8Hz)

5

Example 100

A mixture of N-[2-(4-aminobut-1-yloxy)-4-methylphenyl]-3-methoxy-N-methyl-4-(2-methyl-1H-benzimidazol-4-yl)-carbonylaminobenzamide (150 mg), 37% formaldehyde solution (43.7 mg) and sodium cyanoborohydride (18.3 mg) in methanol (10 ml) was stirred at ambient temperature for 6 hours. The mixture was diluted with chloroform and the solution was washed with saturated aqueous sodium hydrogen carbonate and brine. The organic phase was dried over magnesium sulfate and the solvent was evaporated in vacuo. The crude product was purified by silica gel column (5% methanol in chloroform) to give N-[2-(4-dimethylaminobut-1-yloxy)-4-methylphenyl]-3-methoxy-N-methyl-4-(2-methyl-1H-benzimidazol-4-yl)-carbonylaminobenzamide (142 mg).

15

20

NMR (CDCl<sub>3</sub>, δ) : 1.67-1.87 (4H, m), 2.25 (3H, s), 2.35 (6H, s), 2.46-2.61 (2H, m), 2.61 (3H, s), 3.32 (3H, s), 3.73 (3H, s), 3.81 (1H, m), 3.94 (1H, m), 6.53-6.64 (2H, m), 6.81-7.01 (3H, m), 7.24 (1H, t, J=8Hz), 7.46 (1H, br), 8.03 (1H, br), 8.50 (1H, br)

25

Example 101

The following compound was obtained according to similar manners to those of Preparation 25 and Example 38.

30

N-(2-Amino-4-methylbenzyl)-3-methoxy-N-methyl-4-(2-methylbenzimidazol-4-yl)carbamoylbenzamide dihydrochloride

NMR (DMSO-d<sub>6</sub>, δ) : 2.60 (3H, s), 2.79 (3H, s), 4.00 (3H, s), 4.03 (3H, s), 7.45-7.62 (3H, m), 7.69-7.81 (3H, m), 7.96 (1H, s), 8.03-8.11 (2H, m)

35

Example 102

A mixture of N-(2-carboxy-4-methylphenyl)-3-methoxy-N-methyl-4-(2-methyl-1H-benzimidazol-4-yl)carbonylamino-benzamide (350 mg), diphenylphosphorylazide (224 mg) and  
5 triethylamine (82.5 mg) in dioxane (10 ml) was heated at 80°C for 6 hours. After evaporation, the residual oil was subjected to silica gel column and the column was eluted with 5% methanol in chloroform. Object fractions were collected and evaporated in vacuo and the residue was solidified from  
10 chloroform to give N-(2-amino-4-methylphenyl)-3-methoxy-N-methyl-4-(2-methyl-1H-benzimidazol-4-yl)carbonylamino-benzamide (280 mg).

NMR (DMSO-d<sub>6</sub>, δ) : 2.10 (3H, s), 2.64 (3H, s), 3.11  
(3H, s), 4.80 (3H, s), 5.41 (2H, s), 6.13 (1H, d,  
15 J=8Hz), 6.48-6.55 (2H, m), 7.02 (1H, d, J=8Hz),  
7.09 (1H, s), 7.30 (1H, t, J=8Hz), 7.57 (1H, d,  
J=8Hz), 7.86 (1H, d, J=8Hz), 8.40 (1H, d, J=8Hz)

Example 103

20 The following compound was obtained according to a similar manner to that of Example 102.

N-(2-Amino-4-methylphenyl)-4-(1H-benzimidazol-4-yl)carbonylamino-3-methoxy-N-methylbenzamide

25 NMR (DMSO-d<sub>6</sub>, δ) : 2.08 (3H, s), 3.11 (3H, s), 3.76  
(3H, s), 5.41 (2H, s), 6.14 (1H, d, J=8Hz), 6.47-  
6.53 (2H, m), 7.02 (1H, d, J=8Hz), 7.09 (1H, s),  
7.40 (1H, t, J=8Hz), 7.81 (1H, d, J=8Hz), 7.97 (1H,  
d, J=8Hz), 8.35 (1H, d, J=8Hz), 8.52 (1H, s)

30

Example 104

A mixture of N-[2-(5-carboxypent-1-yloxy)-4-methylphenyl]-3-methoxy-N-methyl-4-[2-(tert-butoxycarbonyl)-aminomethyl-1H-benzimidazol-4-yl]carbonylaminobenzamide (850  
35 mg), N-hydroxysuccinimide (145 mg) and N,N'-dicyclohexyl-

carbodiimide (260 mg) in tetrahydrofuran (20 ml) was stirred at ambient temperature overnight and the resulting insoluble urea was filtered off. To the filtrate was added lithium borohydride (55 mg) and the mixture was stirred at ambient temperature for 5 hours. The mixture was diluted with chloroform and the solution was washed successively with 1N hydrochloric acid, saturated aqueous sodium hydrogen carbonate and brine. The organic phase was dried over magnesium sulfate and the solvent was evaporated in vacuo. The crude product was purified by silica gel column (5% methanol in chloroform) to give N-[2-(6-hydroxyhex-1-yl)oxy-4-methyl]phenyl-3-methoxy-N-methyl-4-[2-(tert-butoxycarbonyl)aminomethyl-1H-benzimidazol-4-yl]carbonylaminobenzamide (340 mg).

NMR (CDCl<sub>3</sub>, δ) : 1.40-1.51 (2H, m), 1.48 (9H, s), 1.57-1.65 (2H, m), 1.71-1.82 (2H, m), 2.25 (3H, s), 3.35 (3H, s), 3.61-3.69 (2H, m), 3.73 (3H, s), 3.80 (1H, m), 3.91 (1H, m), 4.59 (2H, d, J=7Hz), 5.92 (1H, br t, J=7Hz), 6.56-6.63 (2H, m), 6.89-7.01 (3H, m), 7.29 (1H, t, J=8Hz), 7.55 (1H, d, J=8Hz), 7.96 (1H, d, J=8Hz), 8.41 (1H, d, J=8Hz)

#### Example 105

A mixture of N-[2-(6-hydroxyhex-1-yl)oxy-4-methyl]phenyl-3-methoxy-N-methyl-4-[2-(tert-butoxycarbonyl)aminomethyl-1H-benzimidazol-4-yl]carbonylaminobenzamide (210 mg), mesyl chloride (36.5 mg) and triethylamine (32.2 mg) in dichloromethane (10 ml) was stirred in an ice bath for 2 hours. The mixture was diluted with chloroform and the solution was washed successively with 1N hydrochloric acid, saturated aqueous sodium hydrogen carbonate and brine. The organic phase was dried over magnesium sulfate and the solvent was evaporated in vacuo to give N-[2-(6-methanesulfonyloxyhex-1-yl)oxy-4-methyl]phenyl-3-methoxy-N-methyl-4-[2-(tert-butoxycarbonyl)aminomethyl-1H-benzimidazol-4-

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yl]carbonylaminobenzamide (235 mg).

NMR (CDCl<sub>3</sub>, δ) : 1.40-1.56 (4H, m), 1.49 (9H, s), 1.71-1.82 (2H, m), 2.28 (3H, s), 3.00 (3H, s), 3.36 (3H, s), 3.81 (3H, s), 3.81 (1H, m), 3.91 (1H, m), 4.22 (2H, t, J=7.5Hz), 4.58 (2H, d, J=7Hz), 5.61 (1H, br), 6.56-6.63 (2H, m), 6.90 (1H, d, J=8Hz), 6.95 (1H, d, J=8Hz), 7.00 (1H, s), 7.30 (1H, t, J=8Hz), 7.55 (1H, br), 8.10 (1H, br), 8.48 (1H, br)

10 Example 106

A mixture of N-[2-(6-methanesulfonyloxyhex-1-yl)oxy-4-methyl]phenyl-3-methoxy-N-methyl-4-[2-(tert-butoxycarbonyl)-aminomethyl-1H-benzimidazol-4-yl]carbonylaminobenzamide (235 mg) and potassium phthalimide (88.5 mg) in dimethyl sulfoxide (10 ml) was heated at 50°C for 6 hours. The mixture was diluted with ethyl acetate and the solution was washed with water and brine. The organic phase was dried over magnesium sulfate and the solvent was evaporated in vacuo. The crude product was purified by silica gel column (1% methanol in chloroform) to give 3-methoxy-N-methyl-N-[2-(6-phthalimidohex-1-yl)oxy-4-methyl]phenyl-4-[2-(tert-butoxycarbonyl)-aminomethyl-1H-benzimidazol-4-yl]carbonylaminobenzamide (224 mg).

NMR (CDCl<sub>3</sub>, δ) : 1.36-1.54 (4H, m), 1.48 (9H, s), 1.64-1.87 (4H, m), 2.26 (3H, s), 2.61 (3H, s), 3.32 (3H, s), 3.69 (2H, t, J=7.5Hz), 3.79 (3H, s), 3.79 (1H, m), 3.90 (1H, m), 4.60 (1H, d, J=7Hz), 5.72 (1H, br), 6.54-6.63 (2H, m), 6.81-7.01 (3H, m), 7.31 (1H, t, J=8Hz), 7.60 (1H, d, J=8Hz), 7.70 (1H, m), 7.76 (1H, m), 7.80-7.88 (2H, m), 7.99 (1H, br), 8.41 (1H, d, J=8Hz)

Example 107

A solution of 4-[2-chloro-1H-benzimidazol-4-yl]carbonylamino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-

methylnpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide (70 mg) and N-methylnpiperazine (106 mg) was heated at 80°C for 2.5 hours. The excess of N-methylnpiperazine was evaporated in vacuo and the residue was purified by preparative thin-layer chromatography (chloroform:methanol = 10:1) to give 3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylnpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]-4-[2-(4-methylnpiperazin-1-yl)-1H-benzimidazol-4-yl]carbonylaminobenzamide (66 mg).

NMR (CDCl<sub>3</sub>, δ) : 1.43-1.60 (2H, m), 1.62-1.93 (4H, m),  
2.23 (3H, s), 2.27 (3H, s), 2.30-2.43 (9H, m),  
2.47-2.60 (4H, m), 3.34 (3H, s), 3.42-3.52 (2H, m),  
3.54-3.72 (9H, m), 3.74-4.00 (2H, m), 6.50-6.67  
(2H, m), 6.78-7.09 (4H, m), 7.21 (1H, m), 7.92 (1H,  
m), 8.58 (1H, m)

#### Example 108

The following compounds were obtained according to a similar manner to that of Example 107.

- 1) 3-Methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylnpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]-4-[2-(morpholin-4-yl)-1H-benzimidazol-4-yl]carbonylaminobenzamide

NMR (CDCl<sub>3</sub>, δ) : 1.45-1.60 (2H, m), 1.62-1.95 (4H, m),  
2.25 (3H, s), 2.30 (3H, s), 2.32-2.44 (6H, m), 3.33  
(3H, s), 3.41-3.52 (5H, m), 3.53-3.68 (6H, m),  
3.75-4.00 (6H, m), 6.50-6.65 (2H, m), 6.73 (1H, s);  
6.84 (1H, m), 6.91 (1H, m), 7.03 (1H, m), 7.23 (1H,  
m), 7.93 (1H, m), 8.59 (1H, m)

- 2) 4-[(2-Dimethylamino-1H-benzimidazol-4-yl)carbonylamino]-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylnpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide

NMR (CDCl<sub>3</sub>, δ) : 1.42-1.59 (2H, m), 1.61-1.96 (4H, m),  
2.24 (3H, s), 2.29 (3H, s), 2.31-2.44 (6H, m), 3.12  
(6H, s), 3.32 (3H, s), 3.38-3.53 (5H, m), 3.57-3.69



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(2H, m), 3.72-4.00 (2H, m), 6.50-6.64 (2H, m), 6.70  
(1H, s), 6.78-7.08 (3H, m), 7.16-7.29 (1H, m), 7.91  
(1H, m), 8.60 (1H, m), 9.28 (1H, s)

- 5      3) 4-[2-[4-(Dimethylamino)piperidino]-1H-benzimidazol-4-yl]carbonylamino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]-benzamide

10      NMR (CDCl<sub>3</sub>, δ) : 1.29-2.00 (10H, m), 2.19-2.48 (18H, m), 2.67 (1H, m), 2.97-3.16 (2H, m), 3.33 (3H, s), 3.42-4.01 (9H, m), 4.18-4.46 (2H, m), 6.50-6.66 (2H, m), 6.78-7.08 (4H, m), 7.21 (1H, d, J=8Hz), 7.92 (1H, d, J=8Hz), 8.01 (1H, s), 8.59 (1H, m), 9.59 (1H, m)

15

- 4) 4-[[2-(Dimethylamino)amino-1H-benzimidazol-4-yl]-carbonylamino]-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]-benzamide

20      NMR (CDCl<sub>3</sub>, δ) : 1.21-1.36 (2H, m), 1.46-1.70 (4H, m), 2.12-2.38 (12H, m), 3.17 (3H, s), 3.25-3.54 (7H, m), 3.56-3.92 (8H, m), 6.39 (2H, s), 6.50 (1H, s), 6.60 (1H, d, J=8Hz), 6.69 (1H, d, J=8Hz), 6.72 (1H, s), 6.97 (1H, d, J=8Hz), 7.20 (1H, dd, J=8, 8Hz), 7.72 (1H, d, J=8Hz), 7.98 (1H, d, J=8Hz), 8.60 (1H, d, J=8Hz)

25

- 5) 4-[2-[(2-Aminoethyl)methylamino]-1H-benzimidazol-4-yl]-carbonylamino]-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]-benzamide

30      NMR (CDCl<sub>3</sub>, δ) : 1.43-1.59 (2H, m), 1.61-1.90 (4H, m), 2.26 (3H, s), 2.28 (3H, s), 2.30-2.44 (6H, m), 2.98-3.07 (2H, m), 3.29 (3H, s), 3.33 (3H, s), 3.41-3.52 (4H, m), 3.56-3.66 (2H, m), 3.70 (3H, s),

35

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3.77-4.00 (2H, m), 6.52-6.66 (2H, m), 6.80-7.06  
(4H, m), 7.22 (1H, m), 7.89 (1H, m), 8.56 (1H, m)

6) 4-[[2-[[2-(Dimethylamino)ethyl]amino]-1H-benzimidazol-4-  
yl]carbonylamino]-3-methoxy-N-methyl-N-[4-methyl-2-[5-  
(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]-  
benzamide

NMR (CDCl<sub>3</sub>, δ) : 1.43-1.58 (2H, m), 1.62-1.88 (4H, m),  
2.20-2.42 (18H, m), 2.52-2.62 (2H, m), 3.23 (3H,  
s), 3.42-3.56 (4H, m), 3.58-3.67 (2H, m), 3.72 (3H,  
s), 3.77-4.00 (2H, m), 5.69 (1H, m), 6.53-6.65 (2H,  
m), 6.87 (1H, d, J=8Hz), 6.91-7.00 (2H, m), 7.03  
(1H, dd, J=8, 8Hz), 7.24 (1H, d, J=8Hz), 7.82 (1H,  
d, J=8Hz), 8.50 (1H, d, J=8Hz)

#### Example 109

The following compound was obtained by using 3-methoxy-  
N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)-  
carbonylpent-1-yloxy]phenyl]-4-[2-(1-benzyloxycarbonyl-4-  
piperidyl)-1H-benzimidazol-4-yl]carbonylaminobenzamide as a  
starting compound according to a similar manner to that of  
Example 24.

3-Methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-  
1-yl)carbonylpent-1-yloxy]phenyl]-4-[2-(4-piperidyl)-1H-  
benzimidazol-4-yl]carbonylaminobenzamide

NMR (DMSO-d<sub>6</sub>, δ) : 1.37-1.50 (2H, m), 1.50-1.63 (2H,  
m), 1.68-1.81 (2H, m), 1.85-2.04 (2H, m), 2.13 (3H,  
s), 2.15-2.37 (11H, m), 2.83-2.98 (2H, m), 3.11-  
3.49 (10H, m), 3.79 (3H, s), 3.83-4.05 (2H, m),  
6.65 (1H, d, J=8Hz), 6.84 (1H, s), 6.92 (1H, d,  
J=8Hz), 6.96 (1H, s), 7.03 (1H, d, J=8Hz), 7.33  
(1H, t, J=8Hz), 7.70 (1H, d, J=8Hz), 7.91 (1H, d,  
J=8Hz), 8.43 (1H, d, J=8Hz)

Example 110

4-(2-Formyl-1H-benzimidazol-4-yl)carbonylamino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide (158 mg),  
5 hydroxylamine hydrochloride (25 mg), sodium acetate (30 mg) and ethanol (60% solution in water, 1.5 ml) were combined and the mixture was stirred at 60°C for 3 hours. After cooled to ambient temperature, the reaction mixture was concentrated in vacuo. The residue was dissolved in chloroform, washed with  
10 water and brine and dried over magnesium sulfate and evaporated in vacuo. The residue was purified by basic preparative thin-layer chromatography (chloroform:methanol = 15:1) to give 4-(2-syn-hydroxyiminomethyl-1H-benzimidazol-4-yl)carbonylamino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide  
15 (38 mg) and 4-(2-anti-hydroxyiminomethyl-1H-benzimidazol-4-yl)carbonylamino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide (89 mg).

20 Syn isomer :

NMR (DMSO-d<sub>6</sub>, δ) : 1.37-1.49 (2H, m), 1.49-1.63 (2H, m), 1.67-1.80 (2H, m), 2.13 (3H, s), 2.15-2.35 (9H, m), 3.20 (3H, s), 3.35-3.44 (4H, m), 3.76-3.90 (4H, m), 3.90-4.01 (1H, m), 6.65 (1H, d, J=8Hz), 6.82  
25 (1H, s), 6.90-6.98 (2H, m), 7.05 (1H, d, J=8Hz), 7.45 (1H, t, J=8Hz), 7.82 (1H, s), 7.87 (1H, d, J=8Hz), 8.00 (1H, d, J=8Hz), 8.40 (1H, d, J=8Hz)

Anti isomer :

30 NMR (DMSO-d<sub>6</sub>, δ) : 1.37-1.49 (2H, m), 1.49-1.62 (2H, m), 1.67-1.81 (2H, m), 2.12 (3H, s), 2.16-2.35 (9H, m), 3.19 (3H, s), 3.35-3.45 (4H, m), 3.73-3.90 (4H, m), 3.90-4.02 (1H, m), 6.64 (1H, d, J=8Hz), 6.81 (1H, s), 6.89-6.98 (2H, m), 7.04 (1H, d, J=8Hz),  
35 7.43 (1H, t, J=8Hz), 7.72 (1H, d, J=8Hz), 7.96 (1H,

d, J=8Hz), 8.23 (1H, s), 8.40 (1H, d, J=8Hz)

#### Example 111

To a solution of 4-[[2-cyanomethyl-1H-benzimidazol-4-yl]carbonylamino]-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide (224 mg) in ethanol (4 ml) and water (2 ml) was added hydroxylamine hydrochloride (93.5 mg) and sodium hydrogen carbonate (113 mg). The solution was heated at 90°C for 2 hours. After being concentrated in vacuo, aqueous sodium hydrogen carbonate was added to the residue and extracted with ethyl acetate. The extract was washed with brine and dried over sodium sulfate. After evaporation of the solvent, the residue was purified by silica gel column chromatography (10% methanol in chloroform) to give 4-[[2-[(2-amino-2-(hydroxyimino)ethyl]-1H-benzimidazol-4-yl]carbonylamino]-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide (200 mg).

NMR (CDCl<sub>3</sub>, δ) : 1.37-1.58 (2H, m), 1.60-1.87 (4H, m), 2.22-2.49 (12H, m), 3.34 (3H, s), 3.39-3.51 (2H, m), 3.52-4.00 (9H, m), 5.49 (2H, br s), 6.51-6.66 (2H, m), 6.72 (1H, s), 6.81-7.01 (2H, m), 7.17 (1H, dd, J=8, 8Hz), 7.41 (1H, d, J=8Hz), 8.02 (1H, d, J=8Hz), 8.45 (1H, d, J=8Hz)

#### Example 112

To a solution of 4-[(2-formylindol-4-yl)carbonyl]amino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide (200 mg) in pyridine (4.0 ml) was added hydroxylamine hydrochloride (21.3 mg) and the solution was stirred at ambient temperature for 1 hour. The resulting solution was concentrated in vacuo and the residue was diluted with chloroform. The organic layer was washed successively with water and brine, dried over magnesium sulfate and concentrated in vacuo to give 4-[(2-

hydroxyiminomethylindol-4-yl)carbonyl]amino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide (203 mg).

5 NMR (CDCl<sub>3</sub>, δ) : 1.48-1.60 (2H, m), 1.67-1.88 (4H, m),  
2.27 (3H, s), 2.29 (3H, s), 2.32-2.47 (6H, m), 3.34  
(3H, s), 3.48-3.56 (2H, m), 3.61-3.68 (2H, m), 3.70  
(3H, s), 3.82-3.99 (2H, m), 6.57-6.64 (2H, m), 6.88  
(1H, d, J=8Hz), 6.94 (1H, d, J=8Hz), 7.00 (1H, s),  
7.12 (1H, s), 7.22 (1H, t, J=8Hz), 7.44 (1H, d,  
10 J=8Hz), 7.50 (1H, d, J=8Hz), 8.14 (1H, s), 8.32  
(1H, d, J=8Hz), 8.58-8.67 (2H, m), 9.32-9.38 (1H,  
br s)

#### Example 113

15 To a solution of 2-methoxy-4-[N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]-  
carbamoyl]benzoic acid (200 mg) in N,N-dimethylformamide (3  
ml) at 0°C were added 1-ethyl-3-(3-dimethylaminopropyl)-  
carbodiimide hydrochloride (97 mg), N-hydroxybenzotriazole  
20 (79 mg) and 4-amino-2-[(4-methylpiperazin-1-yl)methyl]-1H-  
benzimidazole (105 mg) and the mixture was stirred at ambient  
temperature for 15 hours. The reaction mixture was poured  
into saturated sodium bicarbonate aqueous solution and  
extracted with chloroform. The organic layer was washed with  
25 saturated sodium bicarbonate aqueous solution and brine,  
dried over magnesium sulfate and evaporated in vacuo. The  
residue was purified by preparative thin-layer chromatography  
(chloroform:methanol = 10:1) to give 3-methoxy-N-methyl-N-[4-  
methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]-  
30 phenyl]-4-[2-[(4-methylpiperazin-1-yl)methyl]-1H-  
benzimidazol-4-yl]carbamoylbenzamide (104 mg).

NMR (CDCl<sub>3</sub>, δ) : 1.45-1.63 (2H, m), 1.63-1.79 (2H, m),  
1.79-1.92 (2H, m), 2.28 (3H, s), 2.30-2.60 (12H,  
m), 2.60-3.00 (8H, m), 3.35 (3H, s), 3.46-3.58 (2H,  
35 m), 3.58-3.74 (2H, m), 3.82-4.06 (7H, m), 6.55-6.69

(2H, m), 6.88 (1H, d, J=8Hz), 7.00-7.13 (2H, m),  
7.13-7.41 (2H, m), 8.06 (1H, d, J=8Hz), 8.32 (1H,  
br peak)

5     Example 114

      The following compounds were obtained according to a  
similar manner to that of Example 113.

- 1)   4-(1H-Benzimidazol-4-yl)carbamoyl-3-methoxy-N-methyl-N-  
10   [4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-  
      yloxy]phenyl]benzamide  
      NMR (CDCl<sub>3</sub>, δ) : 1.49-1.60 (2H, m), 1.67-1.90 (4H, m),  
                          2.29 (3H, s), 2.36 (2H, t, J=8Hz), 2.38 (3H, s),  
                          2.42-2.53 (4H, m), 3.36 (3H, s), 3.52-3.58 (2H, m),  
15                        3.60 (3H, s), 3.65-3.73 (2H, m), 3.87-4.00 (2H, m),  
                          4.30-4.39 (2H, m), 6.59-6.68 (3H, m), 6.88 (1H, d,  
                          J=8Hz), 7.01-7.07 (2H, m), 7.16 (1H, t, J=8Hz),  
                          7.28 (1H, d, J=8Hz), 7.38 (1H, d, J=8Hz), 7.68 (1H,  
                          s)  
20
- 2)   4-[(Naphthalen-1-yl)carbamoyl]-3-methoxy-N-methyl-N-[4-  
      methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-  
      yloxy]phenyl]benzamide  
      NMR (CDCl<sub>3</sub>, δ) : 1.50-1.90 (6H, m), 2.28 (3H, s), 2.30  
25                        (3H, s), 2.32-2.41 (6H, m), 3.37 (3H, s), 3.46-3.51  
                          (2H, m), 3.59-3.67 (2H, m), 3.87-3.99 (2H, m), 4.02  
                          (3H, s), 6.58-6.64 (2H, m), 6.88 (1H, d, J=8Hz),  
                          7.02 (1H, d, J=8Hz), 7.16 (1H, s), 7.48-7.58 (3H,  
                          m), 7.68 (1H, d, J=8Hz), 7.86-7.95 (2H, m), 8.10  
30                        (1H, d, J=8Hz), 8.28 (1H, d, J=8Hz)
- 3)   3-(2-Carbamoylphenylcarbamoyl)-3-methoxy-N-methyl-N-[4-  
      methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-  
      yloxy]phenyl]benzamide  
35    NMR (CDCl<sub>3</sub>, δ) : 1.48-1.59 (2H, m), 1.67-1.89 (4H, m),

2.27 (3H, s), 2.30 (3H, s), 2.32-2.43 (6H, m), 3.34 (3H, s), 3.47-3.52 (2H, m), 3.60-3.67 (2H, m), 3.82-3.98 (2H, m), 3.89 (3H, s), 5.84-5.95 (1H, br), 6.56-6.62 (2H, m), 6.87 (1H, d, J=8Hz), 6.95-7.08 (3H, m), 7.44 (1H, d, J=9Hz), 7.50 (1H, d, J=9Hz), 7.93 (1H, d, J=8Hz), 8.63 (1H, d, J=8Hz)

4) 4-(2-Methoxycarbonylphenylcarbamoyl)-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide

NMR (CDCl<sub>3</sub>, δ) : 1.49-1.58 (2H, m), 1.67-1.88 (4H, m), 2.27 (3H, s), 2.37 (2H, t, J=8Hz), 2.55 (3H, s), 2.77-2.88 (4H, m), 3.33 (3H, s), 3.62-3.68 (2H, m), 3.74-3.80 (2H, m), 3.87-3.98 (2H, m), 3.90 (3H, s), 3.92 (3H, s), 6.57-6.60 (2H, m), 6.86 (1H, d, J=8Hz), 6.94 (1H, d, J=8Hz), 7.02 (1H, s), 7.29-7.37 (1H, m), 7.60 (1H, d, J=8Hz), 7.82 (1H, d, J=8Hz), 7.90 (1H, d, J=8Hz), 8.01 (1H, d, J=8Hz), 8.82 (1H, d, J=8Hz)

5) 4-(2-Sulfamoylphenylcarbamoyl)-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide

NMR (CDCl<sub>3</sub>, δ) : 1.47-1.54 (2H, m), 1.64-1.84 (4H, m), 2.28 (3H, s), 2.34 (2H, t, J=8Hz), 2.50 (3H, s), 2.68-2.79 (4H, m), 3.28-3.42 (2H, br), 3.32 (3H, s), 3.58-3.64 (2H, m), 3.72-3.78 (2H, m), 3.82-3.97 (2H, m), 3.88 (3H, s), 6.57-6.61 (2H, m), 6.87 (1H, d, J=8Hz), 6.98 (1H, d, J=8Hz), 7.04 (1H, s), 7.29-7.39 (2H, m), 7.62 (1H, dd, J=2, 8Hz), 7.83 (2H, d, J=8Hz)

6) 4-[(Indol-4-yl)carbamoyl]-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide

NMR (CDCl<sub>3</sub>, δ) : 1.49-1.76 (4H, m), 1.80-1.90 (2H, m),  
2.28 (3H, s), 2.30 (3H, s), 2.32-2.43 (6H, m), 3.38  
(3H, s), 3.47-3.52 (2H, m), 3.60-3.68 (2H, m),  
3.87-3.97 (2H, m), 4.00 (3H, s), 6.48 (1H, s),  
5 6.58-6.64 (2H, m), 6.88 (1H, d, J=8Hz), 7.01 (1H,  
d, J=8Hz), 7.11 (1H, s), 7.18-7.22 (2H, m), 7.23-  
7.32 (1H, br), 8.06-8.11 (2H, m), 8.37-8.41 (1H, br  
s)

- 10 7) 3-Methoxy-N-methyl-4-(2-methyl-1H-benzimidazol-4-  
yl)carbamoyl-N-(4-methyl-2-nitrophenyl)benzamide

NMR (CDCl<sub>3</sub>, δ) : 2.39 (3H, s), 2.59 (3H, s), 3.44 (3H,  
s), 4.01 (3H, s), 6.87 (1H, d, J=8Hz), 7.07 (1H,  
s), 7.11-7.23 (4H, m), 7.34 (1H, m), 7.62 (1H, s),  
15 8.01 (1H, d, J=8Hz)

- 8) 3-Methoxy-N-methyl-4-(2-methyl-1H-benzimidazol-4-  
yl)carbamoyl-N-[2-(4-tert-butoxycarbonylaminobut-1-  
yl)oxy-4-methyl]phenylbenzamide

20 NMR (CDCl<sub>3</sub>, δ) : 1.46 (9H, s), 1.61-1.74 (2H, m), 1.74-  
1.88 (2H, m), 2.25 (3H, s), 2.65 (3H, s), 3.13-3.22  
(2H, m), 3.34 (3H, s), 3.82-3.97 (2H, m), 3.93 (3H,  
s), 4.67 (1H, br), 6.58-6.63 (2H, m), 6.90 (1H, d,  
J=8Hz), 7.00-7.10 (2H, m), 7.17 (1H, t, J=8Hz),  
25 7.30 (1H, m), 7.41 (1H, d, J=8Hz), 8.03 (1H, d,  
J=8Hz)

- 9) 4-[N-[1-[(tert-Butyl)oxycarbonyl]benzamidazol-4-yl]-  
carbamoyl]-N-[2-[4,4-dimethyl(2,5-oxazolinyl)]phenyl]-3-  
30 methoxy-N-methylbenzamide

NMR (CDCl<sub>3</sub>, δ) : 1.37 (3H, s), 1.38 (3H, s), 1.70 (9H,  
s), 3.40 (3H, s), 3.90 (3H, s), 4.02-4.16 (2H, m),  
7.02-7.41 (7H, m), 7.61 (1H, d, J=8Hz), 7.78 (1H,  
d, J=8Hz), 8.08 (1H, dd, J=8, 8Hz), 8.44 (1H, d,  
35 J=8Hz)



- 10) 4-[N-[2-[(Dimethylamino)methyl]-1H-benzimidazol-4-yl]-  
carbamoyl]-N-[2-[4,4-dimethyl(2,5-oxazolinyl)]phenyl]-3-  
methoxy-N-methylbenzamide  
5 NMR (CDCl<sub>3</sub>, δ) : 1.38 (3H, s), 1.39 (3H, s), 2.39 (6H,  
s), 3.39 (3H, s), 3.81 (2H, s), 3.89 (3H, s), 4.07-  
4.17 (2H, m), 7.04-7.39 (8H, m), 7.80 (1H, d,  
J=8Hz), 8.10 (1H, d, J=8Hz)
- 11) 4-[N-[1-[(tert-Butyl)oxycarbonyl]benzimidazol-4-yl]-  
10 carbamoyl]-3-methoxy-N-methyl-N-[2-(morpholin-4-yl)-  
phenyl]benzamide  
NMR (CDCl<sub>3</sub>, δ) : 1.72 (9H, s), 2.32-2.46 (2H, m),  
2.80-2.92 (2H, m), 3.53 (3H, s), 3.63-3.84 (4H, m),  
3.91 (3H, s), 6.88 (1H, d, J=8Hz), 7.05 (1H, s),  
15 7.09-7.25 (3H, m), 7.32 (1H, m), 7.38 (1H, dd, J=8,  
8Hz), 7.64 (1H, d, J=8Hz), 8.10 (1H, d, J=8Hz),  
8.37 (1H, s), 8.47 (1H, d, J=8Hz)
- 12) 4-[N-[1-[(tert-Butyl)oxycarbonyl]benzimidazol-4-yl]-  
20 carbamoyl]-3-methoxy-N-methyl-N-[2-(1-pyrrolyl)phenyl]-  
benzamide  
NMR (CDCl<sub>3</sub>, δ) : 1.72 (9H, s), 3.50 (3H, s), 3.96 (3H,  
s), 6.22-6.31 (2H, m), 6.40-6.49 (2H, m), 6.54-6.69  
(2H, m), 7.06-8.05 (8H, m), 8.38 (1H, s), 8.46 (1H,  
25 d, J=8Hz)
- 13) 3-Methoxy-N-methyl-4-[N-(2-methyl-1H-benzimidazol-4-  
yl)carbamoyl]-N-(2-piperidinophenyl)benzamide  
NMR (CDCl<sub>3</sub>, δ) : 1.41-1.78 (6H, m), 2.26-2.41 (2H, m),  
30 2.60 (3H, s), 2.70-2.86 (2H, m), 3.53 (3H, s),  
3.72-3.93 (3H, m), 6.66-7.57 (9H, m), 8.00-8.39  
(1H, m)
- 14) 4-[N-[1-[(tert-Butyl)oxycarbonyl]-2-methylbenzimidazol-  
35 4-yl]carbamoyl]-3-methoxy-N-methyl-N-[2-(4-methyl-1-

piperazinyl)phenyl]benzamide

NMR (CDCl<sub>3</sub>, δ) : 1.70 (9H, s), 2.38 (3H, s), 2.41-2.65 (6H, m), 2.81 (3H, s), 2.86-3.01 (2H, m), 3.52 (3H, s), 3.89 (3H, s), 6.89 (1H, d, J=8Hz), 6.98 (1H, s), 7.06-7.34 (5H, m), 7.57 (1H, d, J=8Hz), 8.13 (1H, d, J=8Hz), 8.41 (1H, d, J=8Hz)

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- 15) 4-[N-[1-[(tert-Butyl)oxycarbonyl]-2-methylbenzimidazol-4-yl]carbamoyl]-3-methoxy-N-methyl-N-[2-(2,5-oxazolyl)-phenyl]benzamide

NMR (CDCl<sub>3</sub>, δ) : 1.71 (9H, s), 2.81 (3H, s), 3.49 (3H, s), 3.90 (3H, s), 6.79-6.87 (2H, m), 7.17-7.46 (6H, m), 7.56 (1H, d, J=8Hz), 7.78 (1H, s), 7.88 (1H, m), 8.00 (1H, d, J=8Hz), 8.37 (1H, d, J=8Hz)

15

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- 16) 3-Methoxy-N-methyl-4-[N-(2-methyl-1H-benzimidazol-4-yl)carbamoyl]-N-[2-(2,5-oxazoliny)phenyl]benzamide

NMR (CDCl<sub>3</sub>, δ) : 2.60 (3H, br s), 3.44 (3H, s), 3.79-3.96 (3H, m), 4.02-4.16 (2H, m), 4.29-4.49 (2H, m), 6.72 (1H, m), 6.98-7.59 (8H, m), 7.78 (1H, d, J=8Hz), 8.06 (1H, d, J=8Hz)

25

- 17) 3-Methoxy-N-methyl-4-[N-(2-methyl-1H-benzimidazol-4-yl)carbamoyl]-N-[2-(3H,4H,5H-2,6-oxazinyl)phenyl]-benzamide

NMR (CDCl<sub>3</sub>, δ) : 1.93-2.09 (2H, m), 2.52-2.65 (3H, m), 3.43 (3H, s), 3.52-3.65 (2H, m), 3.80 and 3.88 (Total 3H, s), 4.27-4.42 (2H, m), 6.73 (1H, d, J=8Hz), 6.96-8.36 (10H, m)

30

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- 18) N-[2-(1-Aza-3-oxaspiro[4.4]non-1-en-2-yl)phenyl]-3-methoxy-N-methyl-4-[N-(2-methyl-1H-benzimidazol-4-yl)-carbamoyl]benzamide

NMR (CDCl<sub>3</sub>, δ) : 1.62-1.78 (4H, m), 1.83-2.06 (4H, m), 2.60 (3H, s), 3.40 (3H, s), 3.86 (3H, br s), 4.18-

4.29 (2H, m), 6.72 (1H, m), 7.02-7.20 (4H, m),  
7.22-7.40 (2H, m), 7.50 (1H, m), 7.77 (1H, m), 8.07  
(1H, d, J=8Hz)

- 5     19) 3-Methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-  
1-yl)carbonylpent-1-yloxy]phenyl]-4-(2-phthalimido-  
methyl-1H-benzimidazol-4-yl)carbamoylbenzamide

NMR (CDCl<sub>3</sub>, δ) : 1.47-1.67 (2H, m), 1.67-1.80 (2H, m),  
1.80-1.94 (2H, m), 2.23-2.33 (6H, m), 2.33-2.45  
10     (6H, m), 3.38 (3H, s), 3.45-3.55 (2H, m), 3.59-3.71  
(2H, m), 3.81-4.09 (5H, m), 5.15 (2H, s), 6.54-6.68  
(2H, m), 6.76-6.95 (1H, m), 6.98-7.17 (3H, m),  
7.67-7.83 (2H, m), 7.83-7.95 (2H, m), 8.03-8.17  
(1H, m), 8.33 (1H, d, J=8Hz), 9.75-9.83 (1H, m)

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- 20) 3-Methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-  
1-yl)carbonylpent-1-yloxy]phenyl]-4-[2-(2-phthalimido-  
ethyl)-1H-benzimidazol-4-yl]carbamoylbenzamide

NMR (CDCl<sub>3</sub>, δ) : 1.46-1.63 (2H, m), 1.63-1.78 (2H, m),  
1.78-1.91 (2H, m), 2.20-2.49 (9H, m), 2.49-2.71  
20     (3H, m), 3.28-3.43 (5H, m), 3.43-4.04 (9H, m), 4.23  
(2H, t, J=7.5Hz), 6.56-6.69 (2H, m), 6.81-7.11 (3H,  
m), 7.18 (1H, br peak), 7.24-7.33 (1H, m), 7.48  
(1H, br peak), 7.60-7.73 (2H, m), 7.78-7.87 (2H,  
25     m), 8.03 (1H, br peak)

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- 21) 4-(2-tert-Butyldiphenylsiloxymethyl-1H-benzimidazol-4-  
yl)carbamoyl-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-  
methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]-  
30     benzamide

NMR (CDCl<sub>3</sub>, δ) : 1.16 (9H, s), 1.44-1.64 (2H, m),  
1.64-1.79 (2H, m), 1.79-1.94 (2H, m), 2.20-2.31  
(6H, m), 2.31-2.43 (6H, m), 3.33 (3H x 1/2, s),  
3.38 (3H x 1/2, s), 3.44-3.54 (2H, m), 3.57-3.69  
35     (2H, m), 3.77-4.01 (5H, m), 4.99-5.06 (2H, m),

35

6.54-6.68 (2H, m), 6.74-6.94 (2H, m), 6.94-7.32 (3H, m), 7.32-7.59 (6H, m), 7.65-7.77 (4H, m), 8.00-8.14 (1H, m), 8.35 (1H x 1/2, d, J=8Hz), 9.34 (1H x 1/2, s)

5

- 22) 3-Methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]-4-[2-[(tert-butoxy)-carbonylamino]-1H-benzimidazol-4-yl]carbamoylbenzamide

10 NMR (DMSO-d<sub>6</sub>, δ) : 1.36-1.50 (2H, m), 1.50-1.61 (2H, m), 1.66 (9H, s), 1.70-1.80 (2H, m), 2.14 (3H, s), 2.17-2.37 (9H, m), 3.21 (3H, s), 3.38-3.46 (4H, m), 3.79-4.04 (5H, m), 6.65 (1H, d, J=8Hz), 6.80 (1H, s), 6.96 (1H, t, J=8Hz), 7.02 (1H, d, J=8Hz), 7.05-7.14 (2H, m), 7.30 (1H, d, J=8Hz), 7.34 (2H, br peak), 7.90 (1H, d, J=9Hz), 8.11 (1H, d, J=8Hz)

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- 23) 3-Methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]-4-[2-[(methylsulfonyl)amino]-1H-benzimidazol-4-yl]carbamoylbenzamide

20 NMR (DMSO-d<sub>6</sub>, δ) : 1.36-1.50 (2H, m), 1.50-1.64 (2H, m), 1.64-1.82 (2H, m), 2.15 (3H, s), 2.18-2.36 (9H, m), 3.20 (3H, s), 3.37-3.46 (4H, m), 3.49 (3H, s), 3.77-4.03 (5H, m), 6.64 (1H, d, J=8Hz), 6.81 (1H, s), 6.96-7.14 (6H, m), 7.23 (1H, d, J=8Hz), 7.90 (1H, d, J=8Hz), 8.13 (1H, d, J=8Hz)

25

- 24) 3-Methoxy-4-[2-methoxymethyl-1H-benzimidazol-4-yl]-carbamoyl-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide

30 NMR (DMSO-d<sub>6</sub>, δ) : 1.38-1.50 (2H, m), 1.50-1.64 (2H, m), 1.64-1.83 (2H, m), 2.13 (3H, s), 2.16-2.38 (9H, m), 3.20 (3H, s), 3.35-3.47 (7H, m), 3.82-4.01 (5H, m), 4.68 (2H, s), 6.65 (1H, d, J=8Hz), 6.81 (1H, s), 7.00-7.23 (5H, m), 7.91 (1H, d, J=8Hz), 8.11 (1H, d, J=8Hz)

35

- 25) 3-Methoxy-N-methyl-4-[2-methyl-1H-benzimidazol-4-yl]-  
carbamoyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)-  
carbonylpent-1-yloxy]phenyl]benzamide

NMR (DMSO-d<sub>6</sub>, δ) : 1.38-1.51 (2H, m), 1.51-1.66 (2H,  
5 m), 1.66-1.83 (2H, m), 2.15 (3H, s), 2.18-2.38 (9H,  
m), 2.52 (3H, s), 3.22 (3H, s), 3.36-3.48 (4H, m),  
3.80-4.05 (5H, m), 6.64 (1H, d, J=8Hz), 6.81 (1H,  
s), 6.98-7.18 (5H, m), 7.90 (1H, d, J=8Hz), 8.06  
(1H, d, J=8Hz)

10

- 26) 4-[1,2-Dimethyl-1H-benzimidazol-4-yl]carbamoyl-3-  
methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-  
yl)carbonylpent-1-yloxy]phenyl]benzamide

NMR (DMSO-d<sub>6</sub>, δ) : 1.38-1.51 (2H, m), 1.51-1.65 (2H,  
15 m), 1.70-1.82 (2H, m), 2.15 (3H, s), 2.18-2.39 (9H,  
m), 2.56 (3H, s), 3.21 (3H, s), 3.37-3.50 (4H, m),  
3.73 (3H, s), 3.81-4.05 (5H, m), 6.63 (1H, d,  
J=8Hz), 6.81 (1H, s), 6.99-7.25 (5H, m), 7.90 (1H,  
d, J=8Hz), 8.10 (1H, d, J=8Hz)

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- 27) 4-[2-Ethyl-1H-benzimidazol-4-yl]carbamoyl-3-methoxy-N-  
methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)-  
carbonylpent-1-yloxy]phenyl]benzamide

NMR (DMSO-d<sub>6</sub>, δ) : 1.33-1.50 (5H, m), 1.50-1.66 (2H,  
25 m), 1.66-1.83 (2H, m), 2.14 (3H, s), 2.16-2.28 (7H,  
m), 2.28-2.38 (2H, m), 2.87 (2H, q, J=7.5Hz), 3.22  
(3H, s), 3.37-3.46 (4H, m), 3.81-4.02 (5H, m), 6.64  
(1H, d, J=8Hz), 6.81 (1H, s), 7.00-7.17 (5H, m),  
7.93 (1H, d, J=8Hz), 8.09 (1H, d, J=8Hz)

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- 28) 3-Methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-  
1-yl)carbonylpent-1-yloxy]phenyl]-4-[2-(n-propyl)-1H-  
benzimidazol-4-yl]carbamoylbenzamide

NMR (DMSO-d<sub>6</sub>, δ) : 1.00 (3H, t, J=7.5Hz), 1.37-1.50  
35 (2H, m), 1.50-1.65 (2H, m), 1.70-1.94 (4H, m), 2.15

(3H, s), 2.18-2.38 (9H, m), 2.83 (2H, t, J=7.5Hz),  
3.22 (3H, s), 3.36-3.45 (4H, m), 3.81-4.05 (5H, m),  
6.63 (1H, d, J=8Hz), 6.80 (1H, s), 6.99-7.18 (5H,  
m), 7.92 (1H, d, J=8Hz), 8.08 (1H, d, J=8Hz)

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- 29) 4-[2-Isopropyl-1H-benzimidazol-4-yl]carbamoyl-3-methoxy-  
N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)-  
carbonylpent-1-yloxy]phenyl]benzamide

10 NMR (DMSO-d<sub>6</sub>, δ) : 1.35-1.50 (8H, m), 1.50-1.63 (2H,  
m), 1.70-1.81 (2H, m), 2.13 (3H, s), 2.17-2.37 (9H,  
m), 3.10-3.25 (4H, m), 3.36-3.46 (4H, m), 3.80-4.03  
(5H, m), 6.64 (1H, d, J=8Hz), 6.80 (1H, s), 7.00-  
7.18 (5H, m), 7.93 (1H, d, J=8Hz), 8.09 (1H, d,  
J=8Hz)

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- 30) 3-Methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-  
1-yl)carbonylpent-1-yloxy]phenyl]-4-[2-trifluoromethyl-  
1H-benzimidazol-4-yl]carbamoylbenzamide

20 NMR (DMSO-d<sub>6</sub>, δ) : 1.35-1.50 (2H, m), 1.50-1.64 (2H,  
m), 1.69-1.82 (2H, m), 2.14 (3H, s), 2.19-2.38 (9H,  
m), 3.21 (3H, s), 3.37-3.49 (4H, m), 3.82-4.05 (5H,  
m), 6.63 (1H, d, J=8Hz), 6.81 (1H, s), 6.99-7.13  
(3H, m), 7.32-7.42 (2H, m), 7.84-7.96 (1H, m), 8.20  
(1H, br peak)

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- 31) 3-Methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-  
1-yl)carbonylpent-1-yloxy]phenyl]-4-[2-(3-pyridyl)-1H-  
benzimidazol-4-yl]carbamoylbenzamide

30 NMR (DMSO-d<sub>6</sub>, δ) : 1.39-1.50 (2H, m), 1.50-1.66 (2H,  
m), 1.66-1.84 (2H, m), 2.12 (3H, s), 2.16-2.29 (7H,  
m), 2.31 (2H, t, J=5Hz), 3.23 (3H, s), 3.36-3.50  
(4H, m), 3.82-4.02 (2H, m), 4.07 (3H, s), 6.65 (1H,  
d, J=8Hz), 6.82 (1H, s), 7.03 (1H, d, J=8Hz), 7.07-  
7.16 (2H, m), 7.23 (1H, t, J=8Hz), 7.30 (1H, d,  
35 J=8Hz), 7.64 (1H, dd, J=5, 8Hz), 7.95 (1H, d,

J=8Hz), 8.20 (1H, d, J=8Hz), 8.50 (1H, d, J=8Hz),  
8.70 (1H, d, J=5Hz), 9.37 (1H, s)

- 32) 4-[2-(N,N-Dimethylcarbamoyl)-1H-benzimidazol-4-yl]-  
carbamoyl-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-  
methylnpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]-  
benzamide

NMR (CDCl<sub>3</sub>, δ) : 1.44-1.66 (2H, m), 1.66-1.79 (2H,  
m), 1.79-1.92 (2H, m), 2.26 (3H, s), 2.30 (3H, s),  
2.32-2.45 (6H, m), 3.32 (3H, s), 3.36 (3H, s),  
3.43-3.54 (2H, m), 3.59-3.69 (2H, m), 3.82-4.04  
(8H, m), 6.54-6.67 (2H, m), 6.82-6.95 (2H, m),  
6.95-7.06 (1H, m), 7.11 (1H, s), 7.19-7.41 (2H, m),  
8.08 (1H, d, J=8Hz), 8.48 (1H, d, J=8Hz)

- 33) 3-Methoxy-4-[2-methoxy-1H-benzimidazol-4-yl]carbamoyl-N-  
methyl-N-[4-methyl-2-[5-(4-methylnpiperazin-1-yl)-  
carbonylpent-1-yloxy]phenyl]benzamide

NMR (DMSO-d<sub>6</sub>, δ) : 1.35-1.50 (2H, m), 1.50-1.64 (2H,  
m), 1.68-1.83 (2H, m), 2.13 (3H, s), 2.17-2.36 (9H,  
m), 3.21 (3H, s), 3.36-3.45 (4H, m), 3.83-4.02 (5H,  
m), 4.13 (3H, s), 6.64 (1H, d, J=8Hz), 6.81 (1H,  
s), 6.97-7.13 (5H, m), 7.93 (1H, br peak), 8.06  
(1H, br peak)

- 34) 4-[2-(N,N-Dimethylaminomethyl)-1H-benzimidazol-4-yl]-  
carbamoyl-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methyl-  
piperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide

NMR (DMSO-d<sub>6</sub>, δ) : 1.35-1.50 (2H, m), 1.50-1.63 (2H,  
m), 1.68-1.82 (2H, m), 2.15 (3H, s), 2.20-2.38  
(15H, m), 3.20 (3H, s), 3.36-3.46 (4H, m), 3.70  
(3H, s), 3.80-4.03 (5H, m), 6.63 (1H, d, J=8Hz),  
6.80 (1H, s), 6.99-7.19 (5H, m), 7.91 (1H, d,  
J=8Hz), 8.08 (1H, d, J=8Hz)

- 35) 3-Methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]-4-[2-(1-imidazolyl)-methyl-1H-benzimidazol-4-yl]carbamoylbenzamide

5 NMR (CDCl<sub>3</sub>, δ) : 1.45-1.62 (2H, m), 1.62-1.78 (2H, m),  
1.78-1.90 (2H, m), 2.26 (3H, s), 2.35 (2H, t,  
J=7.5Hz), 2.44 (3H, s), 2.54-2.72 (6H, m), 3.33  
(3H, s), 3.57-3.69 (2H, m), 3.69-3.82 (2H, m),  
3.82-4.03 (5H, m), 5.44 (2H, s), 6.53-6.63 (2H, m),  
6.88 (1H, d, J=8Hz), 6.95-7.40 (5H, m), 7.74 (1H,  
10 br peak), 8.80 (1H, d, J=8Hz)

- 36) 3-Methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]-4-[2-(morpholin-4-ylmethyl)-1H-benzimidazol-4-yl]carbamoylbenzamide

15 NMR (DMSO-d<sub>6</sub>, δ) : 1.40-1.52 (2H, m), 1.52-1.65 (2H,  
m), 1.69-1.82 (2H, m), 2.21 (3H, s), 2.31-2.53  
(13H, m), 3.23 (3H, s), 3.27-3.36 (4H, m), 3.58-  
3.67 (4H, m), 3.78 (2H, s), 3.82-4.01 (5H, m), 6.65  
(1H, d, J=8Hz), 6.81 (1H, s), 7.00-7.23 (5H, m),  
20 7.93 (1H, d, J=8Hz), 8.09 (1H, d, J=8Hz)

- 37) 3-Methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]-4-[2-(pyrrolidin-1-ylmethyl)-1H-benzimidazol-4-yl]carbamoylbenzamide

25 NMR (CDCl<sub>3</sub>, δ) : 1.45-1.60 (2H, m), 1.65-1.78 (2H,  
m), 1.78-1.91 (2H, m), 1.91-2.10 (4H, m), 2.27 (3H,  
s), 2.30 (3H, s), 2.32-2.45 (6H, m), 2.95 (4H, br  
peak), 3.35 (3H, s), 3.45-3.53 (2H, m), 3.58-3.68  
(2H, m), 3.79-4.01 (5H, m), 4.21 (2H, br s), 6.52-  
30 6.65 (2H, m), 6.86 (1H, d, J=8Hz), 7.00 (1H, d,  
J=8Hz), 7.09 (1H, s), 7.18-7.29 (3H, m), 8.04 (1H,  
d, J=8Hz)

- 38) 3-Methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]-4-[2-(piperidino-

35



methyl)-1H-benzimidazol-4-yl}carbamoylebenzamide

NMR (CDCl<sub>3</sub>, δ) : 1.33-1.64 (10H, m), 1.69-1.83 (2H, m), 2.14 (3H, s), 2.16-2.36 (9H, m), 2.40-2.49 (4H, m), 3.21 (3H, s), 3.36-3.49 (4H, m), 3.71 (2H, s), 3.80-4.04 (5H, m), 6.65 (1H, d, J=8Hz), 6.81 (1H, s), 6.99-7.21 (5H, m), 7.91 (1H, d, J=8Hz), 8.09 (1H, d, J=8Hz)

39) 4-[2-[2-(Dimethylamino)ethyl]-1H-benzimidazol-4-yl]-carbamoyle-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide

NMR (CDCl<sub>3</sub>, δ) : 1.45-1.95 (8H, m), 2.26 (3H, s), 2.30 (3H, s), 2.32-2.45 (12H, m), 2.79 (2H, t, J=5Hz), 3.11 (2H, t, J=5Hz), 3.36 (3H, s), 3.45-3.55 (2H, m), 3.60-3.67 (2H, m), 3.80-4.02 (5H, m), 6.55-6.64 (2H, m), 6.88 (1H, d, J=8Hz), 7.00-7.10 (2H, m), 7.13-7.26 (2H, m), 7.93 (1H, br peak), 8.08 (1H, d, J=8Hz)

40) 3-Methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]-4-[2-[2-(4-methylpiperazin-1-yl)ethyl]-1H-benzimidazol-4-yl]-carbamoylebenzamide

NMR (DMSO-d<sub>6</sub>, δ) : 1.37-1.50 (2H, m), 1.50-1.64 (2H, m), 1.68-1.82 (2H, m), 2.13 (6H, s), 2.17-2.54 (17H, m), 2.81 (2H, t-like), 3.01 (2H, t-like), 3.21 (3H, s), 3.38-3.48 (4H, m), 3.81-4.02 (5H, m), 6.65 (1H, d, J=8Hz), 6.81 (1H, s), 6.89-7.21 (5H, m), 7.91 (1H, br peak), 8.07 (1H, br peak)

41) 3-Methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]-4-[2-(4-methylpiperazin-1-yl)-1H-benzimidazol-4-yl]carbamoylebenzamide

NMR (DMSO-d<sub>6</sub>, δ) : 1.38-1.50 (2H, m), 1.50-1.64 (2H, m), 1.64-1.82 (2H, m), 2.15 (3H, s), 2.19-2.39

(12H, m), 2.39-2.53 (4H, m), 3.20 (3H, s), 3.36-3.47 (4H, m), 3.47-3.61 (4H, m), 3.82-4.03 (5H, m), 6.63 (1H, d, J=8Hz), 6.80 (1H, s), 6.83-6.98 (2H, m), 7.00 (1H, d, J=8Hz), 7.03-7.13 (2H, m), 7.91 (1H, d, J=8Hz), 8.00 (1H, d, J=8Hz)

42) 4-[2-Dimethylamino-1H-benzimidazol-4-yl]carbamoyl-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide

10 NMR (DMSO-d<sub>6</sub>, δ) : 1.38-1.50 (2H, m), 1.50-1.65 (2H, m), 1.65-1.82 (2H, m), 2.14 (3H, s), 2.18-2.38 (9H, m), 3.11 (6H, s), 3.21 (3H, s), 3.38-3.48 (4H, m), 3.82-4.01 (5H, m), 6.63 (1H, d, J=8Hz), 6.78-6.87 (2H, m), 6.91 (1H, d, J=8Hz), 7.01 (1H, d, J=8Hz), 15 7.03-7.13 (2H, m), 7.91 (1H, d, J=8Hz), 7.99 (1H, d, J=8Hz)

43) 4-[1-(tert-Butoxycarbonyl)-2-[[2-[N-(tert-butoxycarbonyl)-N-methylamino]ethyl]amino]-1H-benzimidazol-4-yl]-carbamoyl-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide

20 NMR (CDCl<sub>3</sub>, δ) : 1.42 (9H, br peak), 1.50-1.64 (2H, m), 1.64-1.78 (11H, m), 1.78-1.93 (2H, m), 2.25 (3H, s), 2.30 (3H, s), 2.32-2.43 (6H, m), 2.93 (3H, s), 25 3.35 (3H, s), 3.44-3.53 (2H, m), 3.58-3.68 (4H, m), 3.73 (2H, br peak), 3.80-4.01 (5H, m), 6.53-6.63 (2H, m), 6.85 (1H, d, J=8Hz), 6.96-7.09 (3H, m), 7.30 (1H, d, J=8Hz), 7.44 (1H, br peak), 8.06 (1H, d, J=8Hz), 8.38 (1H, d, J=8Hz)

30 44) 4-[1-(tert-Butoxycarbonyl)-2-[[2-[(tert-butoxy)carbonylamino]ethyl]methylamino]-1H-benzimidazol-4-yl]carbamoyl-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide

35 NMR (DMSO-d<sub>6</sub>, δ) : 1.21 (9H, s), 1.38-1.50 (2H, m),

- 1.50-1.68 (11H, m), 1.68-1.81 (2H, m), 2.14 (3H, s), 2.18-2.38 (9H, m), 3.05 (3H, s), 3.15-3.28 (5H, m), 3.36-3.46 (4H, m), 3.46-3.56 (2H, m), 3.81-4.01 (5H, m), 6.63 (1H, d, J=8Hz), 6.70-6.82 (2H, m), 7.00-7.13 (4H, m), 7.34 (1H, d, J=8Hz), 7.92 (1H, d, J=8Hz), 8.20 (1H, d, J=8Hz)
- 45) 4-[2-(1-Imidazolyl)-1H-benzimidazol-4-yl]carbamoyl-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide
- NMR (DMSO-d<sub>6</sub>, δ) : 1.36-1.51 (2H, m), 1.51-1.64 (2H, m), 1.69-1.84 (2H, m), 2.13 (3H, s), 2.17-2.38 (9H, m), 3.23 (3H, s), 3.38-3.49 (4H, m), 3.82-4.08 (5H, m), 6.64 (1H, d, J=8Hz), 6.81 (1H, s), 7.03 (1H, d, J=8Hz), 7.08-7.14 (2H, m), 7.17-7.32 (3H, m), 7.92 (2H, br peak), 8.18 (1H, br peak), 8.49 (1H, s)
- 46) 4-[1-(tert-Butoxycarbonyl)-2-[[2-(dimethylamino)ethyl]-amino]-1H-benzimidazol-4-yl]carbamoyl-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)-carbonylpent-1-yloxy]phenyl]benzamide
- NMR (CDCl<sub>3</sub>, δ) : 1.45-1.88 (13H, m), 1.88-1.91 (2H, m), 2.22-2.43 (18H, m), 2.64 (2H, t, J=5Hz), 3.35 (3H, s), 3.45-3.53 (2H, m), 3.60-3.73 (4H, m), 3.80-4.02 (5H, m), 6.54-6.64 (2H, m), 6.86 (1H, d, J=8Hz), 6.95-7.10 (3H, m), 7.34 (1H, d, J=8Hz), 7.44 (1H, br peak), 8.07 (1H, d, J=8Hz), 8.36 (1H, d, J=8Hz)
- 47) 4-[2-[[2-(Dimethylamino)ethyl]methylamino]-1H-benzimidazol-4-yl]carbamoyl-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide
- NMR (DMSO-d<sub>6</sub>, δ) : 1.35-1.50 (2H, m), 1.50-1.63 (2H, m), 1.68-1.82 (2H, m), 2.13 (3H, s), 2.17-2.37 (15H, m), 2.45-2.53 (2H, m), 3.11 (3H, s), 3.21

(3H, s), 3.37-3.48 (4H, m), 3.62 (2H, t, J=5Hz),  
3.79-4.02 (5H, m), 6.64 (1H, d, J=8Hz), 6.76-6.86  
(2H, m), 6.90 (1H, d, J=8Hz), 6.99-7.13 (3H, m),  
7.91 (1H, d, J=8Hz), 7.99 (1H, d, J=8Hz)

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- 48) 3-Methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]-4-[2-(1,2,4-triazol-1-yl)-1H-benzimidazol-4-yl]carbamoylbenzamide

NMR (DMSO-d<sub>6</sub>, δ) : 1.38-1.50 (2H, m), 1.50-1.65 (2H, m), 1.69-1.82 (2H, m), 2.13 (3H, s), 2.17-2.37 (9H, m), 3.21 (3H, s), 3.36-3.45 (4H, m), 3.82-4.05 (5H, m), 6.64 (1H, d, J=8Hz), 6.81 (1H, s), 7.03 (1H, d, J=8Hz), 7.07-7.15 (2H, m), 7.18-7.31 (2H, m), 7.89 (1H, br peak), 8.17 (1H, br peak), 8.46 (1H, s),  
9.40 (1H, s)

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- 49) 4-[2-[(2-Methoxyethyl)amino]-1H-benzimidazol-4-yl]-carbamoyl-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide

NMR (CDCl<sub>3</sub>, δ) : 1.42-1.76 (4H, m), 1.76-1.91 (2H, m), 2.26 (3H, s), 2.30 (3H, s), 2.31-2.45 (6H, m), 3.34 (4H, s), 3.40 (3H, s), 3.45-3.55 (2H, m), 3.55-3.69 (6H, m), 3.79-4.02 (5H, m), 5.17 (1H, br peak), 6.56-6.65 (2H, m), 6.81 (1H, d, J=8Hz), 6.95-7.10 (3H, m), 7.10-7.35 (2H, m), 8.03 (1H, d, J=8Hz)

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#### Example 115

The following compounds were obtained according to a similar manner to that of Example 38.

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- 1) 4-(Imidazo[1,5-a]pyridine-1-carbonyl)amino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)-carbonylpent-1-yloxy]phenyl]benzamide dihydrochloride

NMR (DMSO-d<sub>6</sub>, δ) : 1.39-1.63 (4H, m), 1.70-1.82 (2H, m), 2.22 (3H, s), 2.39 (2H, t, J=8Hz), 2.75 (3H,

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5 s), 2.90-3.08 (3H, m), 3.19 (3H, s), 3.33-3.50 (3H, m), 3.75 (3H, s), 3.88-4.10 (3H, m), 4.40-4.48 (1H, m), 6.66 (1H, d, J=8Hz), 6.80-6.87 (1H, m), 6.90-7.07 (3H, m), 7.25 (1H, t, J=8Hz), 8.08 (1H, d, J=9Hz), 8.27 (1H, d, J=8Hz), 8.52-8.58 (2H, m), 9.52 (1H, s)

10 2) 4-[(2-Ethoxycarbonylindolin-4-yl)carbonyl]amino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide dihydrochloride  
NMR (DMSO-d<sub>6</sub>, δ) : 1.21 (3H, t, J=8Hz), 1.41-1.63 (4H, m), 1.70-1.80 (2H, m), 2.23 (3H, s), 2.74 and 2.75 (Total 3H, s), 2.86-3.07 (3H, m), 3.19 (3H, s), 3.32-3.61 (6H, m), 3.65 (3H, s), 3.83-4.05 (3H, m), 15 4.11 (2H, q, J=8Hz), 4.37-4.49 (2H, m), 6.66 (1H, d, J=8Hz), 6.71 (1H, d, J=8Hz), 6.82 (1H, s), 6.88-6.93 (2H, m), 6.96 (1H, d, J=8Hz), 7.01-7.09 (2H, m), 7.77 (1H, d, J=8Hz), 8.99 (1H, s)

20 3) 4-[(2-Carbamoylindolin-4-yl)carbonyl]amino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)-carbonylpent-1-yloxy]phenyl]benzamide dihydrochloride  
NMR (DMSO-d<sub>6</sub>, δ) : 1.42-1.63 (4H, m), 1.70-1.80 (2H, m), 2.22 (3H, s), 2.40 (2H, t, J=8Hz), 2.74 (3H, s), 2.90-3.05 (3H, m), 3.19 (3H, s), 3.33-3.59 (6H, m), 3.65 (3H, s), 3.92-4.45 (6H, m), 6.67 (1H, d, J=8Hz), 6.80-6.94 (3H, m), 7.01-7.13 (3H, m), 7.19 (1H, s), 7.48 (1H, s), 7.76 (1H, d, J=8Hz), 9.03 (1H, s)

30 4) 4-[(2-Carbamoylindol-4-yl)carbonyl]amino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)-carbonylpent-1-yloxy]phenyl]benzamide hydrochloride  
NMR (DMSO-d<sub>6</sub>, δ) : 1.42-1.63 (4H, m), 1.71-1.81 (2H, m), 2.26 (3H, s), 2.40 (2H, t, J=8Hz), 2.74 (3H, s)

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s), 2.88-3.05 (3H, m), 3.20 (3H, s), 3.28-3.48 (4H, m), 3.68 (3H, s), 3.83-4.02 (3H, m), 6.68 (1H, d, J=8Hz), 6.83 (1H, s), 6.91-6.98 (2H, m), 7.07 (1H, d, J=8Hz), 7.29 (1H, t, J=8Hz), 7.39-7.45 (1H, br s), 7.56 (1H, d, J=8Hz), 7.57 (1H, s), 7.61 (1H, d, J=8Hz), 7.91 (1H, d, J=8Hz), 8.06-8.11 (1H, br s), 9.12 (1H, s)

5) 4-[[2-(N-Methylcarbamoyl)indol-4-yl]carbonyl]amino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide hydrochloride  
NMR (CDCl<sub>3</sub>, δ) : 1.42-1.62 (4H, m) 1.71-1.80 (2H, m), 2.24 (3H, s), 2.40 (2H, t, J=8Hz), 2.74 (3H, s), 2.79 and 2.81 (Total 3H, s), 2.88-3.02 (3H, m), 3.19 (3H, s), 3.27-3.42 (4H, m), 3.67 (3H, s), 3.86-4.10 (3H, m), 6.67 (1H, d, J=8Hz), 6.83 (1H, s), 6.91-6.98 (2H, m), 7.06 (1H, d, J=8Hz), 7.28 (1H, t, J=8Hz), 7.52 (1H, s), 7.54 (1H, d, J=8Hz), 7.62 (1H, d, J=8Hz), 7.90 (1H, d, J=8Hz), 8.57-8.62 (1H, m), 9.11 (1H, s)

6) 4-[(Indolin-4-yl)carbonyl]amino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide dihydrochloride  
NMR (DMSO-d<sub>6</sub>, δ) : 1.40-1.62 (4H, m), 1.70-1.80 (2H, m), 2.23 (3H, s), 2.39 (2H, t, J=8Hz), 2.74 (3H, s), 2.87-3.06 (3H, m), 3.19 (3H, s), 3.30-3.51 (5H, m), 3.63 (3H, s), 3.67 (2H, t, J=8Hz), 3.81-4.10 (4H, m), 4.39-4.48 (1H, m), 6.64 (1H, d, J=8Hz), 6.82 (1H, s), 6.88-6.93 (2H, m), 7.04 (1H, d, J=8Hz), 7.40-7.47 (2H, m), 7.61-7.72 (2H, m), 9.40 (1H, s)

7) 4-[(2-Hydroxymethylindolin-4-yl)carbonyl]amino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-

yl)carbonylpent-1-yloxy]phenyl]benzamide dihydrochloride

NMR (DMSO-d<sub>6</sub>, δ) : 1.40-1.62 (4H, m), 1.69-1.80 (2H, m), 2.23 (3H, s), 2.39 (2H, t, J=8Hz), 2.73 and 2.74 (Total 3H, s), 2.90-3.12 (4H, m), 3.19 (3H, s), 3.30-3.60 (6H, m), 3.64 (3H, s), 3.82-4.12 (5H, m), 4.39-4.49 (1H, m), 6.65 (1H, d, J=9Hz), 6.82 (1H, s), 6.88-6.93 (2H, m), 7.03 (1H, d, J=9Hz), 7.15 (1H, d, J=7Hz), 7.30 (1H, t, J=9Hz), 7.40 (1H, d, J=7Hz), 7.72 (1H, d, J=9Hz), 9.24 (1H, s)

8) 4-[(2-Aminomethylindol-4-yl)carbonyl]amino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)-carbonylpent-1-yloxy]phenyl]benzamide dihydrochloride

NMR (DMSO-d<sub>6</sub>, δ) : 1.42-1.63 (4H, m), 1.70-1.81 (2H, m), 2.24 (3H, s), 2.39 (2H, t, J=8Hz), 2.70 (3H, s), 2.98-3.12 (3H, m), 3.19 (3H, s), 3.28-3.46 (4H, m), 3.69 (3H, s), 3.84-4.02 (3H, m), 4.23 (2H, s), 6.67 (1H, d, J=8Hz), 6.84 (1H, s), 6.90-6.98 (3H, m), 7.05 (1H, d, J=8Hz), 7.22 (1H, t, J=9Hz), 7.56 (1H, d, J=9Hz), 7.62 (1H, d, J=9Hz), 7.93 (1H, d, J=8Hz), 8.68-8.77 (2H, br), 9.08 (1H, s)

9) 4-[(2-Methylindol-4-yl)carbonyl]amino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide hydrochloride

NMR (DMSO-d<sub>6</sub>, δ) : 1.42-1.63 (4H, m), 1.70-1.80 (2H, m), 2.23 (3H, s), 2.39 (2H, t, J=8Hz), 2.43 (3H, s), 2.76 (3H, s), 2.88-3.02 (3H, m), 3.19 (3H, s), 3.28-3.43 (4H, m), 3.70 (3H, s), 3.86-4.07 (3H, m), 6.53 (1H, s), 6.67 (1H, d, J=8Hz), 6.83 (1H, s), 6.90-6.97 (2H, m), 7.06 (1H, d, J=9Hz), 7.11 (1H, d, J=9Hz), 7.49 (2H, d, J=9Hz), 8.02 (1H, d, J=8Hz), 8.98 (1H, s)

10) 4-[(Indolin-6-yl)carbonyl]amino-3-methoxy-N-methyl-N-[4-

methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide dihydrochloride

5 NMR (DMSO-d<sub>6</sub>, δ) : 1.40-1.63 (4H, m), 1.69-1.80 (2H, m), 2.23 (3H, s), 2.39 (2H, t, J=8Hz), 2.73 (3H, s), 2.90-3.07 (2H, m), 3.19 (3H, s), 3.20 (2H, t, J=8Hz), 3.32-3.50 (3H, m), 3.63 (3H, s), 3.70 (2H, t, J=8Hz), 3.82-4.12 (4H, m), 4.38-4.48 (1H, m), 6.65 (1H, d, J=8Hz), 6.82 (1H, s), 6.88-6.95 (2H, m), 7.04 (1H, d, J=8Hz), 7.48 (1H, d, J=8Hz), 7.53  
10 (1H, d, J=8Hz), 7.62 (1H, d, J=8Hz), 7.72 (1H, s), 7.78 (1H, d, J=8Hz), 9.46 (1H, s)

11) 4-[(Indol-6-yl)carbonyl]amino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide hydrochloride  
15 NMR (DMSO-d<sub>6</sub>, δ) : 1.40-1.63 (4H, m), 1.70-1.81 (2H, m), 2.23 (3H, s), 2.40 (2H, t, J=8Hz), 2.73 and 2.74 (Total 3H, s), 2.83-3.06 (3H, m), 3.18 (3H, s), 3.31-3.46 (3H, m), 3.67 (3H, s), 3.82-4.12 (3H, m),  
20 4.39-4.49 (1H, m), 6.50 (1H, s), 6.67 (1H, d, J=8Hz), 6.83 (1H, s), 6.89-6.96 (2H, m), 7.05 (1H, d, J=8Hz), 7.51-7.58 (2H, m), 7.62 (1H, d, J=8Hz), 7.81 (1H, d, J=8Hz), 8.00 (1H, s), 9.18 (1H, s)

25 12) 4-(1H-Benzimidazol-4-yl)carbonyl-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide dihydrochloride  
ESI-MASS : 627.5 (M+H)

30 13) 4-[(Naphthalen-1-yl)carbonyl]-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide hydrochloride  
NMR (DMSO-d<sub>6</sub>, δ) : 1.42-1.66 (4H, m), 1.73-1.83 (2H, m), 2.23 (3H, s), 2.40 (2H, t, J=8Hz), 2.73 (3H, s), 2.86-3.08 (3H, m), 3.22 (3H, s), 3.31-3.48 (3H,  
35



m), 3.87 (3H, s), 3.90-4.02 (3H, m), 4.38-4.50 (1H, m), 6.68 (1H, d, J=8Hz), 6.82 (1H, s), 6.99 (1H, d, J=8Hz), 7.08 (1H, s), 7.12 (1H, d, J=8Hz), 7.49-7.67 (4H, m), 7.77-7.86 (2H, m), 7.93-8.02 (2H, m)

5

- 14) 4-(2-Carbamoylphenylcarbamoyl)-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide hydrochloride

10 NMR (DMSO-d<sub>6</sub>, δ) : 1.40-1.63 (4H, m), 1.70-1.81 (2H, m), 2.22 (3H, s), 2.39 (2H, t, J=8Hz), 2.73 (3H, s), 2.88-3.05 (3H, m), 3.20 (3H, s), 3.30-3.50 (4H, m), 3.80 (3H, s), 3.83-4.00 (3H, m), 6.65 (1H, d, J=8Hz), 6.80 (1H, s), 6.95-7.00 (2H, m), 7.08-7.18 (2H, m), 7.48 (1H, t, J=8Hz), 7.64 (1H, s), 7.69 (1H, d, J=8Hz), 7.77 (1H, d, J=8Hz), 8.18 (1H, s), 8.53 (1H, d, J=8Hz)

15

- 15) 4-(2-Methoxycarbonylphenylcarbamoyl)-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide hydrochloride

20

NMR (DMSO-d<sub>6</sub>, δ) : 1.41-1.62 (4H, m), 1.71-1.80 (2H, m), 2.21 (3H, s), 2.40 (2H, t, J=8Hz), 2.74-2.78 (3H, br s), 2.88-3.02 (3H, m), 3.20 (3H, s), 3.32-3.52 (3H, m), 3.85 (3H, s), 3.88 (3H, s), 3.90-4.12 (3H, m), 4.40-4.48 (1H, m), 6.66 (1H, d, J=8Hz), 6.81 (1H, s), 6.98 (1H, d, J=8Hz), 7.03 (1H, s), 7.09 (1H, d, J=8Hz), 7.21 (1H, t, J=8Hz), 7.63 (1H, t, J=8Hz), 7.72 (1H, d, J=8Hz), 7.79 (1H, d, J=8Hz), 7.98 (1H, d, J=8Hz), 8.67 (1H, d, J=8Hz)

25

30

- 16) 4-[2-(N,N-Dimethylcarbamoyl)phenylcarbamoyl]-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)-carbonylpent-1-yloxy]phenyl]benzamide hydrochloride

35 NMR (DMSO-d<sub>6</sub>, δ) : 1.41-1.63 (4H, m), 1.72-1.81 (2H, m), 2.22 (3H, s), 2.40 (2H, t, J=8Hz), 2.76 (3H,

5 s), 2.83-3.08 (3H, m), 2.89 (3H, s), 3.05 (3H, s),  
3.20 (3H, s), 3.25-3.45 (4H, m), 3.83 (3H, s),  
3.86-4.00 (3H, m), 6.65 (1H, d, J=8Hz), 6.81 (1H,  
s), 6.97-7.02 (2H, m), 7.09 (1H, d, J=8Hz), 7.18  
(1H, t, J=8Hz), 7.35 (1H, d, J=8Hz), 7.42 (1H, t,  
J=8Hz), 7.82 (1H, d, J=8Hz), 8.27 (1H, d, J=8Hz)

10 17) 4-(2-Sulfamoylphenylcarbamoyl)-3-methoxy-N-methyl-N-[4-  
methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-  
yloxy]phenyl]benzamide hydrochloride

15 NMR (DMSO-d<sub>6</sub>, δ) : 1.39-1.62 (4H, m), 1.69-1.79 (2H,  
m), 2.22 (3H, s), 2.38 (2H, t, J=8Hz), 2.77 (3H,  
s), 2.86-3.04 (3H, m), 3.19 (3H, s), 3.35-3.58 (5H,  
m), 3.61 (3H, s), 3.82-4.12 (3H, m), 4.39-4.49 (1H,  
m), 6.63 (1H, d, J=8Hz), 6.80 (1H, s), 6.86-6.92  
(2H, m), 7.06 (1H, d, J=8Hz), 7.39-7.47 (2H, m),  
7.55 (1H, t, J=8Hz), 7.72 (1H, d, J=8Hz), 7.98 (1H,  
d, J=8Hz)

20 18) 4-[(Indol-4-yl)carbamoyl]-3-methoxy-N-methyl-N-[4-  
methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-  
yloxy]phenyl]benzamide hydrochloride

25 NMR (DMSO-d<sub>6</sub>, δ) : 1.42-1.63 (4H, m), 1.72-1.81 (2H,  
m), 2.22 (3H, s), 2.40 (2H, t, J=8Hz), 2.75 (3H,  
s), 2.90-3.03 (3H, m), 3.21 (3H, s), 3.30-3.44 (4H,  
m), 3.88 (3H, s), 3.90-4.00 (3H, m), 6.50 (1H, s),  
6.67 (1H, d, J=8Hz), 6.82 (1H, s), 6.99 (1H, d,  
J=8Hz), 7.04-7.08 (2H, m), 7.12 (1H, d, J=8Hz),  
7.18 (1H, d, J=8Hz), 7.34 (1H, t, J=3Hz), 7.69 (1H,  
30 d, J=8Hz), 7.78 (1H, d, J=8Hz)

19) 3-Methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-  
1-yl)carbonylpent-1-yloxy]phenyl]-4-(quinolin-8-yl)-  
carbonylaminobenzamide dihydrochloride

35 NMR (DMSO-d<sub>6</sub>, δ) : 1.40-1.51 (2H, m), 1.53-1.63 (2H,

- 5 m), 1.70-1.81 (2H, m), 2.23 (3H, s), 2.34-2.42 (2H, m), 2.50 (3H, s), 2.80-3.07 (4H, m), 3.20 (3H, s), 3.31-3.55 (4H, m), 3.83 (3H, s), 4.08 (1H, m), 4.45 (1H, m), 6.65 (1H, d, J=8Hz), 6.82 (1H, s), 6.90-6.99 (2H, m), 7.05 (1H, d, J=8Hz), 7.71-7.85 (2H, m), 8.29 (1H, d, J=8Hz), 8.42 (1H, d, J=8Hz), 8.63 (1H, d, J=8Hz), 8.72 (1H, d, J=8Hz), 9.14 (1H, m)
- 10 20) 3-Methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]-4-(1,2,3,4-tetrahydroquinolin-8-yl)carbonylaminobenzamide dihydrochloride  
NMR (DMSO-d<sub>6</sub>, δ) : 1.39-1.50 (2H, m), 1.52-1.61 (2H, m), 1.68-1.83 (4H, m), 2.23 (3H, s), 2.38 (2H, t, J=7.5Hz), 2.49 (3H, s), 2.80-3.07 (4H, m), 3.18 (3H, s), 3.23-3.50 (6H, m), 3.60 (3H, s), 3.76-4.11 (3H, m), 4.42 (1H, m), 6.50 (1H, t, J=8Hz), 6.64 (1H, d, J=8Hz), 6.82 (1H, s), 6.86-6.92 (2H, m), 7.01-7.04 (2H, m), 7.43 (1H, d, J=8Hz), 7.61 (1H, d, J=8Hz), 9.08 (1H, s)
- 20 21) 3-Methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]-4-(quinoxalin-5-yl)-carbonylaminobenzamide dihydrochloride  
NMR (DMSO-d<sub>6</sub>, δ) : 1.40-1.53 (2H, m), 1.53-1.64 (2H, m), 1.70-1.81 (2H, m), 2.22 (3H, s), 2.40 (2H, t, J=7.5Hz), 2.73 (1H, s), 2.78-3.10 (3H, m), 3.20 (3H, s), 3.30-3.57 (3H, m), 3.65 (3H, s), 3.82-4.11 (3H, m), 4.41 (1H, m), 6.65 (1H, d, J=8Hz), 6.83 (1H, s), 6.88-6.95 (2H, m), 7.04 (2H, d, J=8Hz), 7.64 (1H, d, J=8Hz), 8.20 (1H, d, J=8Hz), 8.30 (1H, d, J=8Hz), 8.60 (1H, s), 9.04 (2H, s), 9.84 (1H, s)
- 30 22) 4-(2-Aminomethyl-1H-benzimidazol-4-yl)carbonylamino-3-methoxy-N-methyl-N-[4-methyl-2-[4-(4-methylpiperazin-1-yl)carbonylphenylmethoxy]phenyl]benzamide
- 35

trihydrochloride

- 23) 4-(2-Aminomethyl-1H-benzimidazol-4-yl)carbonylamino-3-methoxy-N-methyl-N-[4-methyl-2-[3-(4-methylpiperazin-1-yl)carbonylprop-1-yloxy]phenyl]benzamide  
5 trihydrochloride
- 24) 4-(2-Aminomethyl-1H-benzimidazol-4-yl)carbonylamino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylbut-1-yloxy]phenyl]benzamide trihydrochloride  
10 NMR (DMSO-d<sub>6</sub>, δ) : 1.60-1.83 (4H, m), 2.22 (3H, s),  
2.46 (2H, t, J=7.5Hz), 2.72 (3 x 1/2H, s), 2.74 (3  
x 1/2H, s), 2.81-3.09 (3H, m), 3.20 (3H, s), 3.32-  
3.56 (3H, m), 3.70-4.12 (3H, m), 3.77 (3H, s),  
15 4.40-4.50 (3H, m), 6.67 (1H, d, J=8Hz), 6.82 (1H,  
s), 6.94-6.99 (2H, m), 7.08 (1H, d, J=8Hz), 7.43  
(1H, t, J=8Hz), 7.84 (1H, d, J=8Hz), 7.98 (1H, d,  
J=8Hz), 8.29 (1H, d, J=8Hz), 8.88-9.00 (3H, br)
- 20 25) 4-(2-Aminomethyl-1H-benzimidazol-4-yl)carbonylamino-N-[2-[5-[N-(2-dimethylaminoeth-1-yl)-N-methylamino-carbonyl]-pent-1-yloxy]-4-methylphenyl]-3-methoxy-N-methylbenzamide trihydrochloride
- 25 NMR (DMSO-d<sub>6</sub>, δ) : 1.40-1.51 (2H, m), 1.51-1.63 (2H,  
m), 1.69-1.80 (2H, m), 2.22 (3H, s), 2.33 (2H, t,  
J=7.5Hz), 2.74 (3H, s), 2.76 (3H, s), 2.99 (3H, s),  
3.17 (2H, m), 3.19 (3H, s), 3.62 (2H, t, J=7.5Hz),  
3.77 (3H, s), 3.86 (1H, m), 3.97 (1H, m), 4.46 (2H,  
m), 6.66 (1H, d, J=8Hz), 6.84 (1H, s), 6.91-6.97  
30 (2H, m), 7.02 (1H, d, J=8Hz), 7.43 (1H, t, J=8Hz),  
7.83 (1H, d, J=8Hz), 7.97 (1H, d, J=8Hz), 8.29 (1H,  
d, J=8Hz), 8.94 (2H, br)
- 26) N-[2-(5-Carbamoylpent-1-yloxy)-4-methylphenyl]-4-(2-aminomethyl-1H-benzimidazol-4-yl)carbonylamino-3-
- 35

## methoxy-N-methylbenzamide dihydrochloride

- 27) 4-(2-Aminomethyl-1H-benzimidazol-4-yl)carbonylamino-N-[2-[5-(2,2-dimethylhydrazino)carbonylpent-1-yloxy]-4-methylphenyl]-3-methoxy-N-methylcarbonylaminobenzamide trihydrochloride

5 NMR (DMSO-d<sub>6</sub>, δ) : 1.39-1.51 (2H, m), 1.58-1.69 (2H, m), 1.69-1.81 (2H, m), 2.21 (3H, s), 2.25 (2H, t, J=7.5Hz), 3.02 (6H, sx2), 3.19 (3H, s), 3.76 (3H, s), 3.89 (1H, m), 3.99 (1H, m), 4.45 (2H, m), 6.67 10 (1H, d, J=8Hz), 6.83 (1H, s), 6.91-6.96 (2H, m), 7.03 (1H, d, J=8Hz), 7.42 (1H, t, J=8Hz), 7.84 (1H, d, J=8Hz), 7.97 (1H, d, J=8Hz), 8.30 (1H, d, J=8Hz), 8.82-8.98 (3H, br)

15

- 28) N-[2-(4-Aminobut-1-yloxy)-4-methylphenyl]-3-methoxy-N-methyl-4-(2-methyl-1H-benzimidazol-4-yl)-carbonylaminobenzamide dihydrochloride

20 NMR (DMSO-d<sub>6</sub>, δ) : 1.69-1.86 (2H, m), 2.21 (3H, s), 2.76 (3H, s), 2.81-2.92 (2H, m), 3.21 (3H, s), 3.69 (3H, s), 3.89 (1H, m), 4.01 (1H, m), 6.64 (1H, d, J=8Hz), 6.83 (1H, s), 6.90-6.98 (2H, m), 7.02 (1H, d, J=8Hz), 7.51 (1H, t, J=8Hz), 7.88 (1H, d, J=8Hz), 8.01-8.18 (4H, m)

25

- 29) N-[2-(4-Dimethylaminobut-1-yloxy)-4-methylphenyl]-3-methoxy-N-methyl-4-(2-methyl-1H-benzimidazol-4-yl)carbonylaminobenzamide dihydrochloride

30 NMR (DMSO-d<sub>6</sub>, δ) : 1.73-1.89 (4H, m), 2.24 (3H, s), 2.69 (3H, s), 2.70 (3H, s), 2.73 (3H, s), 3.07-3.16 (2H, m), 3.23 (3H, s), 3.67 (3H, s), 3.88 (1H, m), 3.99 (1H, m), 6.68 (1H, d, J=8Hz), 6.83 (1H, s), 6.93 (1H, s), 6.98 (1H, d, J=8Hz), 7.09 (1H, d, J=8Hz), 7.52 (1H, t, J=8Hz), 7.83 (1H, br), 7.90 35 (1H, d, J=8Hz), 8.06 (1H, d, J=8Hz)

- 30) N-[2-(4-Aminobut-1-yl)oxy-4-methyl]phenyl-3-methoxy-N-methyl-4-(2-methyl-1H-benzimidazol-4-yl)-carbamoylbenzamide dihydrochloride

NMR (DMSO-d<sub>6</sub>, δ) : 1.70-1.88 (4H, m), 2.23 (3H, s),  
5 2.78 (3H, s), 2.82-2.92 (2H, m), 3.23 (3H, s), 3.73  
(3H, s), 3.87-6.08 (2H, m), 6.67 (1H, d, J=8Hz),  
6.84 (1H, s), 6.97-7.02 (2H, m), 7.09 (1H, d,  
J=8Hz), 7.45 (1H, t, J=8Hz), 7.55 (1H, d, J=8Hz),  
7.59-7.68 (2H, m), 8.08 (2H, br)

10

- 31) N-[2-(5-Aminopent-1-yl)oxy-4-methyl]phenyl-3-methoxy-N-methyl-4-(2-methyl-1H-benzimidazol-4-yl)-carbonylaminobenzamide dihydrochloride

NMR (DMSO-d<sub>6</sub>, δ) : 1.41-1.51 (2H, m), 1.58-1.69 (2H,  
15 m), 1.69-1.81 (2H, m), 2.23 (3H, s), 2.71 (3H, s),  
2.71-2.82 (2H, m), 3.20 (3H, s), 3.70 (3H, s), 3.88  
(1H, m), 3.98 (1H, m), 6.67 (1H, d, J=8Hz), 6.82  
(1H, s), 6.91 (1H, s), 6.93 (1H, d, J=8Hz), 7.07  
(1H, d, J=8Hz), 7.49 (1H, m), 7.85 (1H, d, J=8Hz),  
20 7.92-8.10 (3H, m)

- 32) N-[2-(6-Aminohex-1-yl)oxy-4-methyl]phenyl-4-(2-aminomethyl-1H-benzimidazol-4-yl)carbonylamino-3-methoxy-N-methylbenzamide trihydrochloride

NMR (DMSO-d<sub>6</sub>, δ) : 1.34-1.50 (4H, m), 1.52-1.65 (2H,  
25 m), 1.70-1.79 (2H, m), 2.21 (3H, s), 2.71-2.80 (2H,  
m), 3.17 (3H, s), 3.75 (3H, s), 3.80-4.20 (2H, m),  
4.41 (2H, m), 6.67 (1H, d, J=8Hz), 7.82 (1H, s),  
6.90-6.98 (2H, m), 7.06 (1H, d, J=8Hz), 7.40 (1H,  
30 t, J=8Hz), 7.83 (1H, d, J=8Hz), 7.90-8.03 (3H, m),  
8.30 (1H, m), 8.82-8.97 (2H, br)

- 33) 3-Methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]-4-[2-(4-methyl-  
35 piperazin-1-yl)-1H-benzimidazol-4-yl]-

carbonylaminobenzamide dihydrochloride

NMR (DMSO-d<sub>6</sub>, δ) : 1.38-1.64 (4H, m), 1.65-1.82 (2H, m), 2.22 (3H, s), 2.39 (2H, t, J=8Hz), 2.68-2.84 (6H, m), 2.85-4.72 (24H, m), 6.65 (1H, d, J=8Hz), 6.82 (1H, s), 6.87-7.00 (2H, m), 7.03 (1H, d, J=8Hz), 7.10 (1H, dd, J=8, 8Hz), 7.45 (1H, d, J=8Hz), 7.74 (1H, d, J=8Hz), 8.40 (1H, d, J=8Hz)

34) 3-Methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]-4-[2-(morpholin-4-yl)-1H-benzimidazol-4-yl]carbonylaminobenzamide dihydrochloride

NMR (DMSO-d<sub>6</sub>, δ) : 1.38-1.66 (4H, m), 1.68-1.83 (2H, m), 2.23 (3H, s), 2.40 (2H, t, J=7Hz), 2.69-2.78 (3H, m), 2.80-3.11 (2H, m), 3.20 (3H, s), 3.28-3.59 (3H, m), 3.60-4.18 (15H, m), 4.42 (1H, m), 6.64 (1H, d, J=8Hz), 6.82 (1H, s), 6.87-6.97 (2H, m), 7.02 (1H, d, J=8Hz), 7.11 (1H, dd, J=8, 8Hz), 7.44 (1H, d, J=8Hz), 7.72 (1H, d, J=8Hz), 8.26 (1H, m), 8.50 (1H, m)

35) 4-[(2-Dimethylamino-1H-benzimidazol-4-yl)carbonylamino]-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide dihydrochloride

NMR (DMSO-d<sub>6</sub>, δ) : 1.37-1.66 (4H, m), 1.68-1.82 (2H, m), 2.22 (3H, s), 2.39 (2H, t, J=7Hz), 2.72 and 2.74 (Total 3H, s), 2.80-3.11 (3H, m), 3.18 (3H, s), 3.21 (6H, s), 3.30-4.18 (9H, m), 4.44 (1H, m), 6.65 (1H, d, J=8Hz), 6.81 (1H, s), 6.87-6.97 (2H, m), 6.97-7.09 (2H, m), 7.35 (1H, d, J=8Hz), 7.68 (1H, d, J=8Hz), 8.37 (1H, m)

36) 4-[2-[4-(Dimethylamino)piperidino]-1H-benzimidazol-4-yl]carbonylamino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-

methylnperazin-1-yl)carbonylpent-1-yloxy]phenyl]-  
benzamide dihydrochloride

NMR (DMSO-d<sub>6</sub>, δ) : 1.32-1.88 (10H, m), 1.99-4.60 (35H,  
m), 6.66 (1H, d, J=8Hz), 6.83 (1H, s), 6.87-7.00  
(2H, m), 7.01-7.12 (2H, m), 7.40 (1H, d, J=8Hz),  
7.71 (1H, d, J=8Hz), 8.00 (1H, s), 8.41 (1H, m)

37) 4-[[2-(Dimethylamino)amino-1H-benzimidazol-4-yl]-  
carbonylamino]-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-  
methylnperazin-1-yl)carbonylpent-1-yloxy]phenyl]-  
benzamide dihydrochloride

NMR (DMSO-d<sub>6</sub>, δ) : 1.37-1.66 (4H, m), 1.67-1.84 (2H,  
m), 2.22 (3H, s), 2.39 (2H, t, J=7Hz), 2.73 (3H,  
s), 2.80-3.11 (3H, m), 3.19 (3H, s), 3.28-4.15  
(15H, m), 4.43 (1H, m), 6.66 (1H, d, J=8Hz), 6.83  
(1H, s), 6.88-7.12 (3H, m), 7.59 (1H, dd, J=8,  
8Hz), 7.92 (1H, d, J=8Hz), 8.10 (1H, d, J=8Hz),  
8.41 (1H, m)

38) 4-[[2-Cyanomethyl-1H-benzimidazol-4-yl]carbonylamino]-3-  
methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylnperazin-1-  
yl)carbonylpent-1-yloxy]phenyl]benzamide dihydrochloride

NMR (DMSO-d<sub>6</sub>, δ) : 1.36-1.66 (4H, m), 1.67-1.83 (2H,  
m), 2.22 (3H, s), 2.39 (2H, t, J=7Hz), 2.72 and  
2.73 (Total 3H, s), 2.80-3.11 (3H, m), 3.20 (3H,  
s), 3.28-3.58 (3H, m), 3.73-4.15 (6H, m), 4.43 (1H,  
m), 4.59 (2H, s), 6.66 (1H, d, J=8Hz), 6.83 (1H,  
s), 6.88-7.00 (2H, m), 7.04 (1H, d, J=8Hz), 7.41  
(1H, dd, J=8, 8Hz), 7.79 (1H, d, J=8Hz), 7.97 (1H,  
d, J=8Hz), 8.39 (1H, d, J=8Hz)

39) 4-[[2-[(2-Amino-2-(hydroxyimino)ethyl]-1H-benzimidazol-  
4-yl]carbonylamino]-3-methoxy-N-methyl-N-[4-methyl-2-[5-  
(4-methylnperazin-1-yl)carbonylpent-1-  
yloxy]phenyl]benzamide trihydrochloride



- 5 NMR (DMSO-d<sub>6</sub>, δ) : 1.37-1.65 (4H, m), 1.66-1.83 (2H, m), 2.22 (3H, s), 2.40 (2H, t, J=7Hz), 2.72 and 2.73 (Total 3H, s), 2.78-3.15 (3H, m), 3.19 (3H, s), 3.24-3.59 (3H, m), 3.77 (3H, s), 3.81-4.17 (3H, m), 4.32 (2H, s), 4.43 (1H, m), 6.66 (1H, d, J=8Hz), 6.83 (1H, s), 6.88-6.99 (2H, m), 7.05 (1H, d, J=8Hz), 7.40 (1H, dd, J=8, 8Hz), 7.80 (1H, d, J=8Hz), 7.96 (1H, d, J=8Hz), 8.29 (1H, d, J=8Hz)
- 10 40) 4-[[2-[(2-Aminoethyl)methylamino]-1H-benzimidazol-4-yl]-carbonylamino]-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]-benzamide trihydrochloride
- 15 NMR (DMSO-d<sub>6</sub>, δ) : 1.37-1.65 (4H, m), 1.66-1.83 (2H, m), 2.22 (3H, s), 2.40 (2H, t, J=7Hz), 2.70 and 2.72 (Total 3H, s), 2.80-3.58 (14H, m), 3.70 (3H, s), 3.77-4.15 (5H, m), 4.43 (1H, m), 6.66 (1H, d, J=8Hz), 6.83 (1H, s), 6.87-6.99 (2H, m), 7.04 (1H, d, J=8Hz), 7.12 (1H, dd, J=8, 8Hz), 7.44 (1H, d, J=8Hz), 7.71 (1H, d, J=8Hz), 8.18 (1H, br), 8.38 (2H, br)
- 20
- 25 41) 4-[[2-[[2-(Dimethylamino)ethyl]amino]-1H-benzimidazol-4-yl]carbonylamino]-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]-benzamide trihydrochloride
- 30 NMR (DMSO-d<sub>6</sub>, δ) : 1.38-1.65 (4H, m), 1.68-1.84 (2H, m), 2.23 (3H, s), 2.39 (2H, t, J=7Hz), 2.65-4.27 (28H, m), 4.42 (1H, m), 6.66 (1H, d, J=8Hz), 6.83 (1H, s), 6.88-6.99 (2H, m), 7.05 (1H, d, J=8Hz), 7.27 (1H, m), 7.55 (1H, d, J=8Hz), 7.83 (1H, d, J=8Hz)
- 35 42) 3-Methoxy-4-(2-mercaptomethyl-1H-benzimidazol-4-yl)-carbonylamino-N-methyl-N-[4-methyl-2-[5-(4-

methylnpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]-  
benzamide dihydrochloride

NMR (DMSO-d<sub>6</sub>, δ) : 1.38-1.66 (4H, m), 1.68-1.84 (2H,  
m), 2.22 (3H, s), 2.39 (2H, t, J=7Hz), 2.70-2.77  
5 (3H, m), 2.79-3.12 (3H, m), 3.20 (3H, s), 3.30-4.18  
(11H, m), 4.36-4.51 (1H, m), 6.66 (1H, d, J=8Hz),  
6.82 (1H, s), 6.88-7.00 (2H, m), 7.05 (1H, d,  
J=8Hz), 7.44 (1H, dd, J=8, 8Hz), 7.81 (1H, d,  
J=8Hz), 8.00 (1H, d, J=8Hz), 8.17 (1H, m)

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43) 4-[2-(3-Hydroxypropyl)-1H-benzimidazol-4-yl]-  
carbonylamino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-  
methylnpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]-  
benzamide dihydrochloride

15

NMR (DMSO-d<sub>6</sub>, δ) : 1.38-1.64 (4H, m), 1.68-1.84 (2H,  
m), 1.94-2.10 (2H, m), 2.22 (3H, s), 2.39 (2H, t,  
J=7Hz), 2.70-2.77 (3H, m), 2.78-3.16 (6H, m), 3.20  
(3H, s), 3.26-3.57 (5H, m), 3.70 (3H, s), 3.79-4.14  
(2H, m), 4.43 (1H, m), 6.66 (1H, d, J=8Hz), 6.83  
20 (1H, s), 6.88-7.00 (2H, m), 7.05 (1H, d, J=8Hz),  
7.46 (1H, m), 7.81 (1H, m), 7.93-8.10 (2H, m)

20

44) 4-[N-(1H-Benzimidazol-4-yl)carbonyl]-N-[2-[4,4-  
dimethyl(2,5-oxazoliny)]phenyl]-3-methoxy-N-  
25 methylbenzamide dihydrochloride

25

NMR (DMSO-d<sub>6</sub>, δ) : 1.30-1.55 (6H, m), 3.30 (3H, s),  
3.67 (3H, s), 3.96-4.11 (1H, m), 4.22-4.38 (1H, m),  
7.00-7.10 (1H, m), 7.17-8.04 (9H, m), 9.60 (1H, s)

30

45) 4-[N-[2-[(Dimethylamino)methyl]-1H-benzimidazol-4-yl]-  
carbonyl]-N-[2-[4,4-dimethyl(2,5-oxazoliny)]phenyl]-3-  
methoxy-N-methylbenzamide trihydrochloride

NMR (DMSO-d<sub>6</sub>, δ) : 1.30-1.56 (6H, m), 2.90 and 2.94  
(Total 6H, s), 3.31 and 3.46 (Total 3H, s), 3.84  
35 and 4.21 (Total 3H, s), 4.42-4.81 (4H, m), 7.06-

35

8.32 (10H, m)

- 46) N-[2-[4,4-Dimethyl(2,5-oxazoliny)]phenyl]-3-methoxy-N-methyl-4-(2-methyl-1H-benzimidazol-4-yl)-  
5 carbonylamino benzamide dihydrochloride  
NMR (DMSO-d<sub>6</sub>, δ) : 1.32-1.51 (6H, m), 2.78 (3H, s),  
3.29 and 3.30 (Total 3H, s), 3.60 (3H, s), 3.92-  
4.16 (1H, m), 4.30-4.49 (1H, m), 6.90-8.36 (10H, m)
- 10 47) 4-[N-(1H-Benzimidazol-4-yl)carbamoyl]-3-methoxy-N-methyl-N-[2-(1-pyrrolyl)phenyl]benzamide hydrochloride  
NMR (DMSO-d<sub>6</sub>, δ) : 3.40 (3H, s), 3.68 (3H, s), 6.23  
(2H, s), 6.52 (2H, s), 6.60 (2H, s), 7.24 (1H, d,  
J=8Hz), 7.30-7.58 (6H, m), 7.62 (1H, d, J=8Hz),  
15 7.71 (1H, d, J=8Hz), 7.84 (1H, d, J=8Hz), 9.46 (1H,  
s)
- 48) 3-Methoxy-N-methyl-4-[N-(2-methyl-1H-benzimidazol-4-yl)-  
carbamoyl]-N-(2-piperidinophenyl)benzamide hydrochloride  
20 NMR (DMSO-d<sub>6</sub>, δ) : 1.38-1.70 (6H, m), 2.16-2.40 (2H,  
m), 2.65-2.89 (5H, m), 3.40 (3H, s), 3.63 (3H, br  
s), 6.83-7.03 (2H, m), 7.04-7.28 (3H, m), 7.40-7.72  
(5H, m)
- 25 49) 3-Methoxy-N-methyl-4-(2-methyl-1H-benzimidazol-4-yl)-  
carbonylamino-N-(2-piperidinophenyl)benzamide  
dihydrochloride  
NMR (DMSO-d<sub>6</sub>, δ) : 1.37-1.72 (6H, m), 2.14-2.43 (2H,  
m), 2.65-2.92 (5H, m), 3.39 (2H, s), 3.59 (3H, br  
30 s), 6.80-7.32 (5H, m), 7.47 (1H, m), 7.58 (1H, dd,  
J=8, 8Hz), 7.70 (1H, m), 7.94 (1H, d, J=8Hz), 8.14  
(1H, d, J=8Hz)
- 50) 3-Methoxy-N-methyl-4-[N-(2-methyl-1H-benzimidazol-4-  
35 yl)carbamoyl]-N-[2-(4-methyl-1-piperazinyl)phenyl]-

benzamide dihydrochloride

NMR (DMSO-d<sub>6</sub>, δ) : 2.78 (3H, s), 2.80-3.26 (9H, m),  
3.30-3.82 (8H, m), 6.90-7.10 (2H, m), 7.14-7.32  
(3H, m), 7.40-7.63 (4H, m), 7.75 (1H, d, J=8Hz)

5

51) 3-Methoxy-N-methyl-4-(2-methyl-1H-benzimidazol-4-yl)-  
carbonylamino-N-[2-(4-methyl-1-piperazinyl)phenyl]-  
benzamide dihydrochloride

10 NMR (DMSO-d<sub>6</sub>, δ) : 2.30 (1H, br s), 2.74 (3H, s), 2.81  
and 2.82 (Total 3H, s), 2.86-3.26 (6H, m), 3.29-  
3.49 (5H, m), 3.60 (3H, s), 6.90-7.02 (2H, m),  
7.11-7.29 (3H, m), 7.42-7.58 (2H, m), 7.78-8.16  
(3H, m)

15 52) 3-Methoxy-N-methyl-4-[N-(2-methyl-1H-benzimidazol-4-yl)-  
carbamoyl]-N-[2-(2,5-oxazolyl)phenyl]benzamide  
hydrochloride

20 NMR (DMSO-d<sub>6</sub>, δ) : 2.77 (3H, s), 3.36 (3H, s), 3.61  
(3H, s), 6.70 (1H, d, J=8Hz), 6.76 (1H, s), 7.37-  
7.69 (8H, m), 7.84 (1H, d, J=8Hz), 8.32 (1H, s)

53) 3-Methoxy-N-methyl-4-[N-(2-methyl-1H-benzimidazol-4-yl)-  
carbamoyl]-N-[2-(2,5-oxazoliny)phenyl]benzamide  
dihydrochloride

25 NMR (DMSO-d<sub>6</sub>, δ) : 2.78 (3H, s), 3.28 (3H, s), 3.38-  
4.11 (7H, m), 7.08-8.80 (10H, m)

54) 3-Methoxy-N-methyl-4-[N-(2-methyl-1H-benzimidazol-4-  
yl) carbamoyl]-N-[2-(3H, 4H, 5H-2,6-oxazinyl)phenyl]-  
benzamide dihydrochloride

30 NMR (DMSO-d<sub>6</sub>, δ) : 1.90-2.06 (2H, m), 2.72-2.85 (3H,  
m), 3.12-4.08 (10H, m), 6.82-8.58 (10H, m)

55) N-[2-(1-Aza-3-oxaspiro[4.4]non-1-en-2-yl)phenyl]-3-  
35 methoxy-N-methyl-4-[N-(2-methyl-1H-benzimidazol-4-

yl)carbamoyl]benzamide dihydrochloride

NMR (DMSO-d<sub>6</sub>, δ) : 1.52-2.07 (8H, m), 2.79 (3H, s),  
3.30 (3H, s), 3.66 (3H, s), 4.38-4.58 (2H, m),  
6.97-7.10 (2H, m), 7.20-8.08 (8H, m)

5

56) 3-Methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]-4-(2-sulfamoylamino-1H-benzimidazol-4-yl)carbonylaminobenzamide dihydrochloride

10 NMR (DMSO-d<sub>6</sub>, δ) : 1.38-1.52 (2H, m), 1.52-1.65 (2H, m), 1.65-1.83 (2H, m), 2.23 (3H, s), 2.39 (2H, t, J=7.5Hz), 2.75 (3H, d, J=4Hz), 2.80-3.08 (3H, m), 3.20 (3H, s), 3.33-3.42 (3H, m), 3.80-3.91 (1H, m), 3.91-4.02 (1H, m), 4.02-4.13 (1H, m), 4.39-4.50  
15 (1H, m), 6.65 (1H, d, J=8Hz), 6.83 (1H, s), 6.89-6.98 (2H, m), 7.04 (1H, d, J=8Hz), 7.21 (1H, t, J=8Hz), 7.38-7.48 (1H, m), 7.54-7.67 (1H, m), 7.77 (1H, d, J=8Hz), 9.61 (1H, br peak), 10.55 (1H, br peak)

20

57) 4-[2-Carbamoyl-1H-benzimidazol-4-yl]carbonylamino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide dihydrochloride

25 NMR (DMSO-d<sub>6</sub>, δ) : 1.39-1.52 (2H, m), 1.52-1.65 (2H, m), 1.65-1.81 (2H, m), 2.23 (3H, s), 2.39 (2H, t, J=7.5Hz), 2.77 (3H, d, J=5Hz), 2.83-3.10 (3H, m), 3.20 (3H, s), 3.31-3.48 (3H, m), 3.77 (3H, s), 3.81-3.92 (1H, m), 3.92-4.01 (1H, m), 4.10 (1H, br d, J=15Hz), 4.45 (1H, br d, J=15Hz), 6.66 (1H, d, J=8Hz),  
30 6.83 (1H, s), 6.91-7.03 (2H, m), 7.07 (1H, d, J=8Hz), 7.51 (1H, t, J=8Hz), 7.71 (1H, s), 7.80 (1H, d, J=8Hz), 8.04 (1H, d, J=8Hz), 8.30 (1H, s), 8.37 (1H, d, J=8Hz), 10.46 (1H, br peak), 12.00 (1H, s)

35

58) 4-[2-(N,N-Dimethylcarbamoyl)-1H-benzimidazol-4-yl]-  
carbonylamino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-  
methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]-  
benzamide dihydrochloride

5 NMR (DMSO-d<sub>6</sub>, δ) : 1.40-1.52 (2H, m), 1.52-1.66 (2H,  
m), 1.70-1.82 (2H, m), 2.22 (3H, s), 2.40 (2H, t,  
J=8Hz), 2.77 (3H, s), 2.83-3.10 (3H, m), 3.15 (3H,  
s), 3.20 (3H, s), 3.33-3.60 (6H, m), 3.72 (3H, s),  
3.80-3.93 (1H, m), 3.93-4.02 (1H, m), 4.02-4.15  
10 (1H, m), 4.40-4.50 (1H, m), 6.65 (1H, d, J=8Hz),  
6.82 (1H, s), 6.88-6.98 (2H, m), 7.05 (1H, d,  
J=8Hz), 7.49 (1H, t, J=8Hz), 7.80 (1H, d, J=8Hz),  
8.03 (1H, d, J=8Hz), 8.30 (1H, d, J=8Hz)

15 59) 3-Methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-  
1-yl)carbonylpent-1-yloxy]phenyl]-4-[2-(4-piperidyl)-1H-  
benzimidazol-4-yl]carbonylaminobenzamide  
trihydrochloride

20 NMR (DMSO-d<sub>6</sub>, δ) : 1.40-1.53 (2H, m), 1.53-1.65 (2H,  
m), 1.70-1.84 (2H, m), 2.03-2.20 (2H, m), 2.23 (3H,  
s), 2.32-2.48 (4H, m), 2.75 (3H, d, J=5Hz), 2.83-  
3.15 (4H, m), 3.19 (3H, s), 3.30-3.54 (7H, m), 3.77  
(3H, s), 3.88 (1H, br peak), 3.97 (1H, br peak),  
4.09 (1H, br d, J=15Hz), 4.44 (1H, br d, J=15Hz),  
25 6.65 (1H, d, J=8Hz), 6.83 (1H, s), 6.90-7.00 (2H,  
m), 7.05 (1H, d, J=8Hz), 7.36 (1H, t, J=8Hz), 7.74  
(1H, d, J=8Hz), 7.93 (1H, d, J=8Hz), 8.37 (1H, br  
d, J=8Hz), 8.97 (1H, br peak), 9.27 (1H, br peak),  
11.05 (1H, br peak)

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60) 4-(2-Aminomethyl-1-methyl-1H-benzimidazol-4-yl)-  
carbonylamino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-  
methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]-  
benzamide trihydrochloride

35 NMR (DMSO-d<sub>6</sub>, δ) : 1.40-1.53 (2H, m), 1.53-1.67 (2H,

- 5 m), 1.70-1.84 (2H, m), 2.23 (3H, s), 2.40 (2H, t, J=7.5Hz), 2.74 (3H, d, J=5Hz), 2.80-3.10 (3H, m), 3.20 (3H, s), 3.32-3.54 (3H, m), 3.68-4.03 (8H, m), 4.10 (1H, br d, J=15Hz), 4.44 (1H, br d, J=15Hz), 4.51-4.61 (2H, m), 6.66 (1H, d, J=8Hz), 6.83 (1H, s), 6.91-7.00 (2H, m), 7.06 (1H, d, J=8Hz), 7.50 (1H, t, J=8Hz), 7.93 (1H, d, J=8Hz), 8.03 (1H, d, J=8Hz), 8.30 (1H, d, J=8Hz), 8.83-8.96 (3H, m)
- 10 61) 4-(2-Aminomethyl-3-methyl-3H-benzimidazol-4-yl)-carbonylamino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]-benzamide trihydrochloride
- 15 NMR (DMSO-d<sub>6</sub>-D<sub>2</sub>O,  $\delta$ ) : 1.41-1.53 (2H, m), 1.53-1.68 (2H, m), 1.68-1.85 (2H, m), 2.26 (3H, s), 2.41 (2H, t, J=7.5Hz), 2.80 (3H, s), 2.86-3.14 (3H, m), 3.21 (3H, s), 3.35-3.52 (2H, m), 3.68 (1H, s), 3.75 (3H, s), 3.84-4.05 (2H, m), 4.05-4.19 (1H, m), 4.42-4.53 (3H, m), 6.70 (1H, d, J=8Hz), 6.87 (1H, s), 6.91-
- 20 7.01 (2H, m), 7.10 (1H, d, J=8Hz), 7.33 (1H, t, J=8Hz), 7.49 (1H, d, J=8Hz), 7.78 (1H, d, J=8Hz), 7.84 (1H, d, J=8Hz)
- 25 62) 4-(2-Methylthio-1H-benzimidazol-4-yl)carbonylamino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide dihydrochloride
- 30 NMR (CDCl<sub>3</sub>,  $\delta$ ) : 1.40-1.52 (2H, m), 1.52-1.66 (2H, m), 1.66-1.82 (2H, m), 2.23 (3H, s), 2.40 (2H, t, J=7Hz), 2.75 (3H, d, J=5Hz), 2.80-3.08 (5H, m), 3.20 (3H, s), 3.33-3.49 (3H, m), 3.72 (3H, s), 3.87 (1H, br peak), 3.95 (1H, br peak), 4.10 (1H, br d, J=15Hz), 4.44 (1H, br d, J=15Hz), 6.65 (1H, d, J=8Hz), 6.81 (1H, s), 6.89-6.99 (2H, m), 7.04 (1H, d, J=8Hz), 7.30 (1H, t, J=8Hz), 7.63 (1H, d, J=8Hz), 7.88 (1H, d, J=8Hz), 8.39 (1H, d, J=8Hz)
- 35

- 63) 3-Methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]-4-(2-methylsulfonyl-1H-benzimidazol-4-yl)carbonylaminobenzamide dihydrochloride
- 5 NMR (DMSO-d<sub>6</sub>, δ) : 1.36-1.51 (2H, m), 1.51-1.66 (2H, m), 1.66-1.83 (2H, m), 2.21 (3H, s), 2.40 (2H, t, J=7.5Hz), 2.76 (3H, d, J=5Hz), 2.81-3.10 (3H, m), 3.19 (3H, s), 3.30-3.68 (6H, m), 3.80 (3H, s), 3.88 (1H, br peak), 3.96 (1H, br peak), 4.09 (1H, br d, J=15Hz),
- 10 4.45 (1H, br d, J=15Hz), 6.65 (1H, d, J=8Hz), 6.81 (1H, s), 6.90-7.00 (2H, m), 7.04 (1H, d, J=8Hz), 7.64 (1H, t, J=8Hz), 7.90 (1H, d, J=8Hz), 8.13 (1H, d, J=8Hz), 8.40 (1H, d, J=8Hz)
- 15 64) 3-Methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]-4-(2-sulfamoyl-1H-benzimidazol-4-yl)carbonylaminobenzamide dihydrochloride
- NMR (DMSO-d<sub>6</sub>, δ) : 1.39-1.52 (2H, m), 1.52-1.67 (2H, m), 1.70-1.83 (2H, m), 2.22 (3H, s), 2.40 (2H, t, J=7.5Hz), 2.76 (3H, d, J=5Hz), 2.85-3.09 (3H, m),
- 20 3.20 (3H, s), 3.33-3.45 (3H, m), 3.75 (3H, s), 3.87 (1H, br peak), 3.97 (1H, br peak), 4.10 (1H, br d, J=15Hz), 4.44 (1H, br d, J=15Hz), 6.64 (1H, d, J=8Hz), 6.83 (1H, s), 6.89 (1H, s), 6.96 (1H, d, J=8Hz),
- 25 7.04 (1H, d, J=8Hz), 7.56 (1H, t, J=8Hz), 7.83 (1H, d, J=8Hz), 8.07 (1H, d, J=8Hz), 8.20 (2H, s), 8.36 (1H, d, J=8Hz)
- 30 65) 4-(2-Aminomethyl-1H-benzimidazol-4-yl)carbonyl-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide trihydrochloride
- NMR (DMSO-d<sub>6</sub>, δ) : 1.40-1.52 (2H, m), 1.52-1.68 (2H, m), 1.68-1.84 (2H, m), 2.22 (3H, s), 2.41 (2H, t, J=6Hz), 2.75 (3H, d, J=5Hz), 2.81-3.10 (3H, m),
- 35



3.22 (3H, s), 3.32-3.52 (4H, m), 3.82-4.02 (4H, m),  
4.09 (1H, br d, J=12Hz), 4.30-4.50 (3H, m), 6.65  
(1H, d, J=8Hz), 6.81 (1H, s), 7.02 (1H, d, J=8Hz),  
7.07-7.16 (2H, m), 7.21 (1H, t, J=8Hz), 7.31 (1H,  
5 d, J=8Hz), 7.88 (1H, d, J=8Hz), 8.05 (1H, br peak),  
8.64-8.75 (3H, m)

66) 4-[2-(2-Aminoethyl)-1H-benzimidazol-4-yl]carbamoyl-3-  
methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-  
10 yl)carbonylpent-1-yloxy]phenyl]benzamide  
trihydrochloride

NMR (DMSO-d<sub>6</sub>, δ) : 1.39-1.52 (2H, m), 1.52-1.67 (2H,  
m), 1.71-1.84 (2H, m), 2.22 (3H, s), 2.41 (2H, t,  
J=7.5Hz), 2.80-3.09 (3H, m), 3.21 (3H, d, J=5Hz),  
15 3.27-3.74 (7H, m), 3.74-4.03 (5H, m), 4.09 (1H, br  
d, J=15Hz), 4.44 (1H, br d, J=15Hz), 6.65 (1H, d,  
J=8Hz), 6.82 (1H, s), 6.99 (1H, d, J=8Hz), 7.06  
(1H, s), 7.11 (1H, d, J=8Hz), 7.26-7.49 (2H, m),  
7.65-7.80 (1H, m), 7.90-7.93 (1H, m), 8.26 (3H, br  
20 peak)

67) 4-(2-Hydroxymethyl-1H-benzimidazol-4-yl)carbamoyl-3-  
methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-  
yl)carbonylpent-1-yloxy]phenyl]benzamide dihydrochloride

25 NMR (DMSO-d<sub>6</sub>, δ) : 1.41-1.52 (2H, m), 1.52-1.66 (2H,  
m), 1.71-1.85 (2H, m), 2.22 (3H, s), 2.40 (2H, t,  
J=7.5Hz), 2.76 (3H, s), 2.82-3.09 (3H, m), 3.21  
(3H, s), 3.79 (3H, s), 3.85-4.03 (2H, m), 4.03-4.15  
(1H, m), 4.38-4.51 (1H, m), 4.91 (2H, s), 6.66 (1H,  
30 d, J=8Hz), 6.84 (1H, s), 7.00 (1H, d, J=8Hz), 7.04  
(1H, s), 7.11 (1H, d, J=8Hz), 7.36-7.52 (2H, m),  
7.63-7.72 (1H, m), 7.72-7.84 (1H, m)

68) 4-[2-Amino-1H-benzimidazol-4-yl]carbamoyl-3-methoxy-N-  
35 methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)-

carbonylpent-1-yloxy]phenyl]benzamide dihydrochloride

NMR (DMSO-d<sub>6</sub>, δ) : 1.40-1.53 (2H, m), 1.53-1.68 (2H, m), 1.70-1.85 (2H, m), 2.23 (3H, s), 2.40 (2H, t, J=7.5Hz), 2.73 (3H, d, J=5Hz), 2.80-3.09 (3H, m), 3.20 (3H, s), 3.30-3.60 (3H, m), 3.71 (3H, s), 3.84-4.02 (2H, m), 4.08 (1H, br d, J=15Hz), 4.43 (1H, br d, J=15Hz), 6.65 (1H, d, J=8Hz), 6.83 (1H, s), 6.97 (1H, d, J=8Hz), 7.01 (1H, s), 7.10 (1H, d, J=8Hz), 7.16-7.23 (2H, m), 7.30-7.38 (1H, m), 7.54 (1H, d, J=8Hz), 8.37 (2H, s)

69) 3-Methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]-4-[2-[(methylsulfonyl)amino]-1H-benzimidazol-4-yl]carbamoylbenzamide dihydrochloride

NMR (DMSO-d<sub>6</sub>, δ) : 1.38-1.52 (2H, m), 1.52-1.67 (2H, m), 1.67-1.83 (2H, m), 2.22 (3H, s), 2.40 (2H, t, J=7.5Hz), 2.76 (3H, d, J=5Hz), 2.82-3.08 (3H, m), 3.23 (3H, s), 3.32-3.48 (3H, m), 3.51 (3H, s), 3.75-4.23 (6H, m), 4.45 (1H, br d, J=15Hz), 6.65 (1H, d, J=8Hz), 6.80 (1H, s), 6.97-7.15 (4H, m), 7.15-7.30 (2H, m), 7.88 (1H, d, J=8Hz), 8.10 (1H, d, J=8Hz)

70) 3-Methoxy-4-[2-methoxymethyl-1H-benzimidazol-4-yl]-carbamoyl-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide dihydrochloride

NMR (DMSO-d<sub>6</sub>, δ) : 1.39-1.52 (2H, m), 1.52-1.67 (2H, m), 1.67-1.85 (2H, m), 2.23 (3H, s), 2.40 (2H, t, J=7.5Hz), 2.74 (3H, d, J=5Hz), 2.80-3.10 (3H, m), 3.21 (3H, s), 3.26-3.54 (6H, m), 3.77 (3H, s), 3.81-4.20 (3H, m), 4.43 (1H, br d, J=15Hz), 4.90 (2H, s), 6.65 (1H, d, J=8Hz), 6.83 (1H, s), 7.00 (1H, d, J=8Hz), 7.03 (1H, s), 7.11 (1H, d, J=8Hz),

7.40-7.58 (2H, m), 7.66 (1H, d, J=8Hz), 7.79 (1H, d, J=8Hz)

- 71) 3-Methoxy-N-methyl-4-[2-methyl-1H-benzimidazol-4-yl]carbamoyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)-carbonylpent-1-yloxy]phenyl]benzamide dihydrochloride  
5 NMR (DMSO-d<sub>6</sub>, δ) : 1.41-1.53 (2H, m), 1.53-1.67 (2H, m), 1.72-1.85 (2H, m), 2.23 (3H, s), 2.40 (2H, t, J=7.5Hz), 2.73 (3H, t, J=5Hz), 2.78 (3H, s), 2.82-3.13 (3H, m), 3.21 (3H, s), 3.30-3.56 (3H, m), 3.75 (3H, s), 3.80-4.17 (3H, m), 4.43 (1H, br d, J=15Hz), 6.65 (1H, d, J=8Hz), 6.84 (1H, s), 6.98 (1H, d, J=8Hz), 7.02 (1H, s), 7.10 (1H, d, J=8Hz), 7.40-7.65 (4H, m)  
10
- 72) 4-[1,2-dimethyl-1H-benzimidazol-4-yl]carbamoyl-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide dihydrochloride  
15 NMR (DMSO-d<sub>6</sub>, δ) : 1.39-1.53 (2H, m), 1.53-1.65 (2H, m), 1.71-1.85 (2H, m), 2.22 (3H, s), 2.40 (2H, t, J=7.5Hz), 2.67-2.80 (6H, m), 2.80-3.10 (3H, m), 3.21 (3H, s), 3.25-3.64 (3H, m), 3.73-4.20 (9H, m), 4.38-4.50 (1H, m), 6.65 (1H, d, J=8Hz), 6.81 (1H, s), 6.95-7.08 (2H, m), 7.11 (1H, d, J=8Hz), 7.45 (1H, br peak), 7.54-7.82 (3H, s)  
20
- 73) 4-[2-Ethyl-1H-benzimidazol-4-yl]carbamoyl-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide dihydrochloride  
25 NMR (DMSO-d<sub>6</sub>, δ) : 1.37-1.52 (5H, m), 1.52-1.68 (2H, m), 1.71-1.85 (2H, m), 2.23 (3H, s), 2.40 (2H, t, J=7.5Hz), 2.75 (3H, s), 2.80-3.17 (5H, m), 3.21 (3H, s), 3.31-3.61 (3H, m), 3.77 (3H, s), 3.85-4.01 (2H, m), 4.09 (1H, br d, J=15Hz), 4.44 (1H, br d, J=15Hz), 6.66 (1H, d, J=8Hz), 6.83 (1H, s), 6.99  
30  
35

(1H, d, J=8Hz), 7.03 (1H, s), 7.11 (1H, d, J=8Hz),  
7.43 (1H, br peak), 7.53 (1H, br peak), 7.66 (2H,  
br peak)

- 5      74)    3-Methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-  
1-yl)carbonylpent-1-yloxy]phenyl]-4-[2-(n-propyl)-1H-  
benzimidazol-4-yl]carbamoylbenzamide dihydrochloride

NMR (DMSO-d<sub>6</sub>, δ) : 0.97 (3H, t, J=7.5Hz), 1.40-1.53  
                  (2H, m), 1.53-1.69 (2H, m), 1.69-1.84 (4H, m), 2.22  
10               (3H, s), 2.39 (2H, t, J=7.5Hz), 2.75 (3H, s), 2.80-  
                  3.14 (5H, m), 3.20 (3H, s), 3.30-3.60 (3H, m), 3.78  
                  (3H, s), 3.83-4.16 (3H, m), 4.04 (1H, br peak),  
                  6.65 (1H, d, J=8Hz), 6.83 (1H, s), 7.00 (1H, d,  
                  J=8Hz), 7.03 (1H, s), 7.10 (1H, d, J=8Hz), 7.43  
15               (1H, br peak), 7.52 (1H, br peak), 7.66 (2H, br  
                  peak)

- 75)    4-[2-Isopropyl-1H-benzimidazol-4-yl]carbamoyl-3-methoxy-  
N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)-  
20               carbonylpent-1-yloxy]phenyl]benzamide dihydrochloride

NMR (DMSO-d<sub>6</sub>, δ) : 1.40-1.53 (8H, m), 1.53-1.69 (2H,  
                  m), 1.69-1.88 (2H, m), 2.23 (3H, s), 2.40 (2H, t,  
                  J=7.5Hz), 2.73 (3H, d, J=5Hz), 2.80-3.08 (3H, m),  
                  3.21 (3H, s), 3.31-3.56 (4H, m), 3.76 (3H, s),  
25               3.85-4.03 (2H, m), 4.09 (1H, br d, J=15Hz), 4.43  
                  (1H, d, J=15Hz), 6.66 (1H, d, J=8Hz), 6.83 (1H, s),  
                  6.98 (1H, d, J=8Hz), 7.02 (1H, s), 7.10 (1H, d,  
                  J=8Hz), 7.39-7.69 (3H, m), 7.80 (1H, br peak)

- 30      76)    3-Methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-  
1-yl)carbonylpent-1-yloxy]phenyl]-4-[2-trifluoromethyl-  
1H-benzimidazol-4-yl]carbamoylbenzamide dihydrochloride

NMR (DMSO-d<sub>6</sub>, δ) : 1.40-1.52 (2H, m), 1.52-1.68 (2H,  
                  m), 1.68-1.83 (2H, m), 2.21 (3H, s), 2.40 (2H, t,  
                  J=7.5Hz), 2.76 (3H, d, J=5Hz), 2.83-3.13 (3H, m),  
35

3.22 (3H, s), 3.33-3.63 (3H, m), 3.82-4.02 (4H, m),  
4.09 (1H, br d, J=15Hz), 4.45 (1H, br d, J=15Hz),  
6.64 (1H, d, J=8Hz), 6.81 (1H, s), 7.00-7.16 (3H,  
m), 7.32-7.46 (2H, m), 7.90 (1H, br peak), 8.23  
5 (1H, br peak)

77) 3-Methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-  
1-yl)carbonylpent-1-yloxy]phenyl]-4-[2-(3-pyridyl)-1H-  
benzimidazol-4-yl]carbamoylbenzamide trihydrochloride

10 NMR (DMSO-d<sub>6</sub>, δ) : 1.41-1.53 (2H, m), 1.53-1.66 (2H,  
m), 1.73-1.85 (2H, m), 2.21 (3H, s), 2.41 (2H, t,  
J=7.5Hz), 2.74 (3H, d, J=5Hz), 2.81-3.08 (3H, m),  
3.23 (3H, s), 3.31-3.51 (3H, m), 3.71-4.16 (6H, m),  
4.40-4.52 (1H, m), 6.66 (1H, d, J=8Hz), 6.81 (1H,  
15 s), 7.04 (1H, d, J=8Hz), 7.08-7.16 (2H, m), 7.29  
(1H, t, J=8Hz), 7.38 (1H, d, J=8Hz), 7.85 (1H, dd,  
J=5, 8Hz), 7.90 (1H, d, J=8Hz), 8.19 (1H, d,  
J=8Hz), 8.77 (1H, d, J=8Hz), 8.83 (1H, d, J=5Hz),  
9.48 (1H, s)

20

78) 4-[2-(N,N-Dimethylcarbamoyl)-1H-benzimidazol-4-yl]-  
carbamoyl-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methyl-  
piperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide  
dihydrochloride

25 NMR (DMSO-d<sub>6</sub>, δ) : 1.38-1.52 (2H, m), 1.52-1.65 (2H,  
m), 1.65-1.83 (2H, m), 2.22 (3H, s), 2.40 (2H, t,  
J=7.5Hz), 2.74 (3H, d, J=5Hz), 2.79-3.07 (3H, m),  
3.11 (3H, s), 3.21 (3H, s), 3.31-3.49 (3H, m), 3.71  
(3H, s), 3.82-4.01 (4H, m), 4.01-4.38 (2H, m), 4.45  
30 (1H, d, J=15Hz), 6.65 (1H, d, J=8Hz), 6.80 (1H, s),  
7.02 (1H, d, J=8Hz), 7.06-7.17 (2H, m), 7.24-7.31  
(2H, m), 7.84-7.93 (1H, m), 8.19-8.29 (1H, m)

79) 4-[2-(N,N-Dimethylaminomethyl)-1H-benzimidazol-4-yl]-  
35 carbamoyl-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-

methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]-  
benzamide trihydrochloride

5 NMR (DMSO-d<sub>6</sub>, δ) : 1.38-1.53 (2H, m), 1.53-1.67 (2H,  
m), 1.67-1.84 (2H, m), 2.20 (3H, s), 2.40 (2H, t,  
J=7.5Hz), 2.74 (3H, d, J=5Hz), 2.80-3.10 (9H, m),  
3.21 (3H, s), 3.31-3.45 (3H, m), 3.81-4.01 (4H, m),  
4.08 (1H, br d, J=15Hz), 4.44 (1H, br d, J=15Hz),  
4.61 (2H, s), 6.65 (1H, d, J=8Hz), 6.81 (1H, s),  
7.02 (1H, d, J=8Hz), 7.07-7.15 (2H, m), 7.24 (1H,  
10 t, J=8Hz), 7.34 (1H, d, J=8Hz), 7.88 (1H, d,  
J=8Hz), 8.10 (1H, br peak)

80) 3-Methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-  
1-yl)carbonylpent-1-yloxy]phenyl]-4-[2-(1-imidazolyl)-  
15 methyl-1H-benzimidazol-4-yl]carbamoylbenzamide  
trihydrochloride

20 NMR (DMSO-d<sub>6</sub>, δ) : 1.40-1.53 (2H, m), 1.53-1.68 (2H,  
m), 1.68-1.85 (2H, m), 2.22 (3H, s), 2.40 (2H, t,  
J=7.5Hz), 2.74 (3H, s), 2.80-3.10 (3H, m), 3.23  
(3H, s), 3.31-3.54 (3H, m), 3.70-4.20 (6H, m), 4.44  
(1H, br peak), 5.84 (2H, s), 6.65 (1H, d, J=8Hz),  
6.82 (1H, s), 7.01 (1H, d, J=8Hz), 7.04-7.15 (2H,  
m), 7.21 (1H, t, J=8Hz), 7.30 (1H, d, J=8Hz), 7.78  
(1H, s-like), 7.87 (1H, d, J=8Hz), 7.92 (1H,  
25 s-like), 8.08 (1H, br peak), 9.40 (1H, s)

81) 3-Methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-  
1-yl)carbonylpent-1-yloxy]phenyl]-4-[2-[(4-methyl-  
piperazin-1-yl)methyl]-1H-benzimidazol-4-yl]-  
30 carbamoylbenzamide trihydrochloride

35 NMR (DMSO-d<sub>6</sub>, δ) : 1.40-1.53 (2H, m), 1.53-1.64 (2H,  
m), 1.70-1.83 (2H, m), 2.23 (3H, s), 2.40 (2H, t,  
J=7.5Hz), 2.70-3.18 (9H, m), 3.21 (3H, s), 3.32-  
4.20 (19H, m), 4.43 (1H, br d, J=15Hz), 6.66 (1H,  
d, J=8Hz), 6.84 (1H, s), 7.00 (1H, d, J=8Hz), 7.05

(1H, s), 7.10 (1H, d, J=8Hz), 7.37 (1H, br peak),  
7.45 (1H, br peak), 7.70 (1H, br peak), 7.89 (1H,  
br peak)

- 5      82)    3-Methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-  
1-yl)carbonylpent-1-yloxy]phenyl]-4-[2-(morpholin-4-  
ylmethyl)-1H-benzimidazol-4-yl]carbamoylbenzamide  
trihydrochloride

10                      NMR (DMSO-d<sub>6</sub>, δ) : 1.39-1.52 (2H, m), 1.52-1.66 (2H,  
m), 1.66-1.85 (2H, m), 2.21 (3H, s), 2.40 (2H, t,  
J=7.5Hz), 2.74 (3H, d, J=5Hz), 2.78-3.11 (3H, m),  
3.21 (3H, s), 3.30-4.00 (16H, m), 4.09 (1H, d,  
J=15Hz), 4.44 (1H, d, J=15Hz), 4.64 (2H, s), 6.65  
(1H, d, J=8Hz), 6.82 (1H, s), 7.03 (1H, d, J=8Hz),  
15                      7.06-7.15 (2H, m), 7.26 (1H, t, J=8Hz), 7.36 (1H,  
d, J=8Hz), 7.87 (1H, d, J=8Hz), 8.08 (1H, br peak)

- 83)    3-Methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-  
1-yl)carbonylpent-1-yloxy]phenyl]-4-[2-(pyrrolidin-1-  
20                      ylmethyl)-1H-benzimidazol-4-yl]carbamoylbenzamide  
trihydrochloride

25                      NMR (DMSO-d<sub>6</sub>, δ) : 1.39-1.53 (2H, m), 1.53-1.68 (2H,  
m), 1.68-1.87 (2H, m), 1.87-2.11 (4H, m), 2.21 (3H,  
s), 2.40 (2H, t, J=7.5Hz), 2.74 (3H, d, J=5Hz),  
2.80-3.11 (3H, m), 3.21 (3H, s), 3.25-3.79 (7H, m),  
3.79-4.02 (5H, m), 4.09 (1H, br d, J=15Hz), 4.44  
(1H, br d, J=15Hz), 4.70 (2H, s), 6.65 (1H, d,  
J=8Hz), 6.81 (1H, s), 7.01 (1H, d, J=8Hz), 7.04-  
7.15 (2H, m), 7.24 (1H, t, J=8Hz), 7.32 (1H, d,  
30                      J=8Hz), 7.87 (1H, d, J=8Hz), 8.03-8.13 (1H, m)

- 84)    3-Methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-  
1-yl)carbonylpent-1-yloxy]phenyl]-4-[2-(piperidino-  
methyl)-1H-benzimidazol-4-yl]carbamoylbenzamide  
35                      trihydrochloride

NMR (DMSO-d<sub>6</sub>, δ) : 1.38-1.90 (12H, m), 2.21 (3H, s),  
2.40 (2H, t, J=7.5Hz), 2.75 (3H, d, J=5Hz), 2.80-  
3.17 (3H, m), 3.23 (3H, s), 3.28-4.02 (15H, m),  
4.09 (1H, br d, J=15Hz), 4.44 (1H, br d, J=15Hz),  
4.59 (2H, s), 6.64 (1H, d, J=8Hz), 6.81 (1H, s),  
7.02 (1H, d, J=8Hz), 7.06-7.15 (2H, m), 7.24 (1H,  
t, J=8Hz), 7.34 (1H, d, J=8Hz), 7.87 (1H, d,  
J=8Hz), 8.09 (1H, br peak)

- 10 85) 4-[2-[2-(Dimethylamino)ethyl]-1H-benzimidazol-4-yl]-  
carbamoyl-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-  
methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]-  
benzamide trihydrochloride

15 NMR (DMSO-d<sub>6</sub>, δ) : 1.39-1.52 (2H, m), 1.52-1.67 (2H,  
m), 1.70-1.86 (2H, m), 2.22 (3H, s), 2.40 (2H, t,  
J=7.5Hz), 2.75 (3H, d, J=5Hz), 2.81-3.08 (9H, m),  
3.22 (3H, s), 3.28-3.72 (7H, m), 3.82-4.02 (5H, m),  
4.09 (1H, br d, J=15Hz), 4.43 (1H, br d, J=15Hz),  
6.65 (1H, d, J=8Hz), 6.81 (1H, s), 7.01 (1H, d,  
20 J=8Hz), 7.05-7.17 (2H, m), 7.20-7.40 (2H, m), 7.80  
(1H, d, J=8Hz), 7.93 (1H, br peak)

- 25 86) 3-Methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-  
1-yl)carbonylpent-1-yloxy]phenyl]-4-[2-[2-(4-  
methylpiperazin-1-yl)ethyl]-1H-benzimidazol-4-yl]-  
carbamoylbenzamide trihydrochloride

30 NMR (DMSO-d<sub>6</sub>, δ) : 1.40-1.53 (2H, m), 1.53-1.66 (2H,  
m), 1.71-1.86 (2H, m), 2.22 (3H, s), 2.40 (2H, t,  
J=7.5Hz), 2.70-2.79 (6H, m), 2.79-3.65 (21H, m),  
3.78-4.01 (5H, m), 4.09 (1H, br d, J=15Hz), 4.44  
(1H, br d, J=15Hz), 6.65 (1H, d, J=8Hz), 6.82 (1H,  
s), 7.00 (1H, d, J=8Hz), 7.05 (1H, s), 7.10 (1H, d,  
J=8Hz), 7.35 (1H, t, J=8Hz), 7.46 (1H, d, J=8Hz),  
7.66-7.80 (2H, m)



- 87) 3-Methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]-4-[2-(4-methylpiperazin-1-yl)-1H-benzimidazol-4-yl]carbamoylbenzamide trihydrochloride
- 5 NMR (DMSO-d<sub>6</sub>, δ) : 1.48-1.53 (2H, m), 1.53-1.65 (2H, m), 1.70-1.85 (2H, m), 2.21 (3H, s), 2.40 (2H, t, J=7.5Hz), 2.74 (3H, d, J=5Hz), 2.80 (3H, s), 2.83-3.10 (3H, m), 3.16-3.83 (13H, m), 3.83-4.15 (2H, m), 4.33 (1H, br d, J=15Hz), 4.43 (1H, br d, J=15Hz), 6.65 (1H, d, J=8Hz), 6.81 (1H, s), 6.96 (1H, d, J=8Hz), 7.01 (1H, s), 7.09 (1H, d, J=8Hz), 7.13-7.24 (2H, m), 7.61 (1H, br peak), 7.79 (1H, br peak)
- 10
- 15 88) 4-[2-Dimethylamino-1H-benzimidazol-4-yl]carbamoyl-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide hydrochloride
- NMR (DMSO-d<sub>6</sub>, δ) : 1.41-1.52 (2H, m), 1.52-1.67 (2H, m), 1.71-1.83 (2H, m), 2.22 (3H, s), 2.40 (2H, t, J=7.5Hz), 2.75 (3H, s), 2.80-3.10 (3H, m), 3.15 (6H, s), 3.21 (3H, s), 3.70-4.50 (6H, m), 4.50 (1H, br peak), 6.65 (1H, d, J=8Hz), 6.82 (1H, s), 6.95-7.06 (2H, m), 7.11 (1H, d, J=8Hz), 7.50-8.10 (4H, m)
- 20
- 25 89) 3-Methoxy-N-methyl-4-[2-[[2-(methylamino)ethyl]amino]-1H-benzimidazol-4-yl]carbamoyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]-benzamide trihydrochloride
- NMR (DMSO-d<sub>6</sub>, δ) : 1.40-1.53 (2H, m), 1.53-1.65 (2H, m), 1.65-1.84 (2H, m), 2.22 (3H, s), 2.40 (2H, t, J=7.5Hz), 2.61 (2H, t-like, J=5Hz), 2.74 (3H, d, J=5Hz), 2.78-3.11 (3H, m), 3.11-3.29 (5H, m), 3.29-3.55 (3H, m), 3.72 (3H, s), 3.73-4.01 (2H, m), 4.09 (1H, br d, J=15Hz), 4.43 (1H, br d, J=15Hz), 6.65 (1H, d, J=8Hz), 6.83 (1H, s), 6.95 (1H, d, J=8Hz),
- 30
- 35

7.00 (1H, s), 7.10 (1H, d, J=8Hz), 7.18-7.27 (2H, m), 7.47-7.61 (2H, m), 9.10 (3H, br peak)

- 5 90) 4-[2-[(2-Aminoethyl)methylamino]-1H-benzimidazol-4-yl]-  
carbamoyl-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-  
methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]-  
benzamide trihydrochloride  
NMR (DMSO-d<sub>6</sub>, δ) : 1.40-1.53 (2H, m), 1.53-1.67 (2H,  
m), 1.70-1.83 (2H, m), 2.23 (3H, s), 2.40 (2H, t,  
10 J=7.5Hz), 2.74 (3H, d, J=5Hz), 2.79-3.11 (3H, m),  
3.11-3.23 (5H, m), 3.26 (3H, s), 3.33-3.56 (5H, m),  
3.71 (3H, s), 3.84-4.02 (5H, m), 4.09 (1H, br d,  
J=15Hz), 4.43 (1H, br d, J=15Hz), 6.65 (1H, d,  
J=8Hz), 6.82 (1H, s), 6.93 (1H, d, J=8Hz), 6.99  
15 (1H, s), 7.09 (1H, d, J=8Hz), 7.18-7.28 (2H, m),  
7.50 (1H, br peak), 7.80 (1H, br peak), 8.29 (3H,  
br peak)
- 20 91) 4-[2-(1-Imidazolyl)-1H-benzimidazol-4-yl]carbamoyl-3-  
methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-  
yl)carbonylpent-1-yloxy]phenyl]benzamide  
trihydrochloride  
NMR (DMSO-d<sub>6</sub>, δ) : 1.41-1.52 (2H, m), 1.52-1.67 (2H,  
m), 1.67-1.84 (2H, m), 2.20 (3H, s), 2.40 (2H, t,  
25 J=7.5Hz), 2.74 (3H, s-like), 2.81-3.10 (3H, m),  
3.22 (3H, s), 3.30-3.53 (3H, m), 3.78-4.22 (6H, m),  
4.39-4.51 (1H, m), 6.66 (1H, d, J=8Hz), 6.81 (3H,  
s), 7.04 (1H, d, J=8Hz), 7.09-7.19 (2H, m), 7.23-  
7.40 (2H, m), 7.65 (1H, s), 7.91 (1H, d, J=8Hz),  
30 8.15-8.29 (2H, m), 9.28 (1H, s)
- 35 92) 4-[2-[[2-(Dimethylamino)ethyl]amino]-1H-benzimidazol-4-  
yl]carbamoyl-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-  
methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]-  
benzamide trihydrochloride

NMR (DMSO-d<sub>6</sub>, δ) : 1.39-1.52 (2H, m), 1.52-1.66 (2H, m), 1.70-1.85 (2H, m), 2.22 (3H, s), 2.40 (2H, t, J=7.5Hz), 2.73 (3H, d, J=5Hz), 2.84 (6H, s), 2.88-3.10 (3H, m), 3.20 (3H, s), 3.28-3.53 (7H, m), 3.84-4.02 (5H, m), 4.08 (1H, br d, J=15Hz), 4.43 (1H, br d, J=15Hz), 6.66 (1H, d, J=8Hz), 6.83 (1H, s), 6.92-7.02 (2H, m), 7.10 (1H, d, J=8Hz), 7.19-7.27 (2H, m), 7.50 (1H, d, J=8Hz), 7.58 (1H, br peak), 9.14 (1H, br peak)

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93) 4-[2-[[2-(Dimethylamino)ethyl]methylamino]-1H-benzimidazol-4-yl]carbamoyl-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]benzamide trihydrochloride

15

NMR (DMSO-d<sub>6</sub>, δ) : 1.41-1.53 (2H, m), 1.53-1.66 (2H, m), 1.70-1.85 (2H, m), 2.22 (3H, s), 2.40 (2H, d, J=7.5Hz), 2.74 (3H, d, J=5Hz), 2.81-3.09 (9H, m), 3.21 (3H, s), 3.26 (3H, s), 3.32-3.55 (7H, m), 3.71 (3H, br s), 3.81-4.14 (3H, m), 4.44 (1H, br d, J=15Hz), 6.65 (1H, d, J=8Hz), 6.82 (1H, s), 6.92 (1H, d, J=8Hz), 6.98 (1H, s), 7.09 (1H, d, J=8Hz), 7.15-7.25 (2H, m), 7.49 (1H, br peak), 7.85 (1H, br peak)

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25 94) 3-Methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]-4-[2-(1,2,4-triazol-1-yl)-1H-benzimidazol-4-yl]carbamoylbenzamide trihydrochloride

30

NMR (DMSO-d<sub>6</sub>, δ) : 1.40-1.53 (2H, m), 1.53-1.67 (2H, m), 1.72-1.85 (2H, m), 2.22 (3H, s), 2.41 (2H, t, J=7.5Hz), 2.76 (3H, d, J=5Hz), 2.80-3.10 (3H, m), 3.21 (3H, s), 3.28-3.64 (3H, m), 3.83-4.03 (5H, m), 4.10 (1H, br d, J=15Hz), 4.45 (1H, br d, J=15Hz), 6.66 (1H, d, J=8Hz), 6.83 (1H, s), 7.05 (1H, d, J=8Hz), 7.08-7.17 (2H, m), 7.21-7.32 (2H, m), 7.90.

35

(1H, br peak), 8.19 (1H, br peak), 8.50 (1H, s),  
9.41 (1H, s)

- 5 95) 4-[2-[(2-Methoxyethyl)amino]-1H-benzimidazol-4-yl]-  
carbamoyl-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-  
methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]-  
benzamide dihydrochloride  
NMR (DMSO-d<sub>6</sub>, δ) : 1.39-1.52 (2H, m), 1.52-1.67 (2H,  
10 m), 1.70-1.85 (2H, m), 2.22 (3H, s), 2.40 (2H, t,  
J=7.5Hz), 2.73 (3H, s), 2.80-3.10 (3H, m), 3.21  
(3H, s), 3.27-3.49 (6H, m), 3.53-3.64 (4H, m), 3.73  
(3H, s), 3.84-4.16 (3H, m), 4.43 (1H, br peak),  
6.65 (1H, d, J=8Hz), 6.84 (1H, s), 6.97 (1H, d,  
15 J=8Hz), 7.00 (1H, s), 7.10 (1H, d, J=8Hz), 7.16-  
7.26 (2H, m), 7.40 (1H, br peak), 7.55 (1H, br  
peak), 8.80 (1H, br peak)

- 20 96) 4-(2-Dimethylaminomethyl-1H-benzimidazol-4-yl)-  
carbonylamino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-  
methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]-  
benzamide trihydrochloride  
NMR (DMSO-d<sub>6</sub>, δ) : 1.40-1.52 (2H, m), 1.52-1.63 (2H,  
m), 1.72-1.82 (2H, m), 2.22 (3H, s), 2.40 (2H, t,  
J=7Hz), 2.73 (3H, s), 2.90-3.05 (10H, m), 3.20 (3H,  
25 s), 3.35-3.50 (3H, m), 3.78 (3H, s), 3.95-4.13 (2H,  
m), 4.40-4.45 (1H, m), 4.68 (2H, s), 6.64 (1H, d,  
J=8Hz), 6.82 (1H, s), 6.90-6.95 (2H, m), 7.04 (1H,  
d, J=8Hz), 7.46 (1H, t, J=8Hz), 7.89 (1H, d,  
J=8Hz), 8.01 (1H, d, J=8Hz), 8.30 (1H, d, J=8Hz)

- 30 97) 3-Methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-  
1-yl)carbonylpent-1-yloxy]phenyl]-4-[2-(4-methyl-  
piperazin-1-yl)methyl-1H-benzimidazol-4-yl]-  
carbonylaminobenzamide trihydrochloride  
35 NMR (DMSO-d<sub>6</sub>, δ) : 1.42-1.52 (2H, m), 1.52-1.64 (2H,

5 m), 1.73-1.82 (2H, m), 2.22 (3H, s), 2.40 (2H, t, J=7Hz), 2.72 (3H, s), 2.77 (3H, s), 2.85-3.10 (4H, m), 3.20 (3H, s), 3.20-3.40 (7H, m), 3.45-3.56 (4H, m), 3.78 (3H, s), 3.83-4.10 (2H, m), 4.37-4.43 (3H, m), 6.65 (1H, d, J=8Hz), 6.82 (1H, s), 6.90-6.93 (2H, m), 7.03 (1H, d, J=8Hz), 7.47 (1H, t, J=8Hz), 7.87 (1H, d, J=8Hz), 8.03 (1H, d, J=8Hz), 8.20-8.23 (1H, m).

10 98) 4-[2-(4-Dimethylaminopiperidino)methyl-1H-benzimidazol-4-yl]carbonylamino-3-methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]-benzamide trihydrochloride

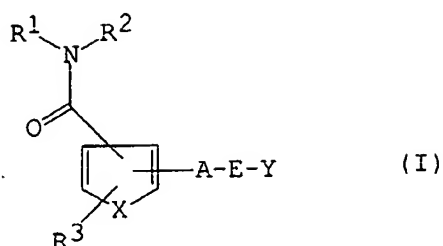
15 NMR (DMSO-d<sub>6</sub>, δ) : 1.40-1.53 (2H, m), 1.53-1.66 (2H, m), 1.70-1.82 (2H, m), 2.10-2.35 (7H, m), 2.42 (2H, t, J=7Hz), 2.63-2.73 (7H, m), 2.85-3.08 (4H, m), 3.18 (3H, s), 3.33-3.53 (3H, m), 3.73-4.30 (9H, m), 4.40-4.47 (1H, m), 4.69 (2H, s), 6.63 (1H, d, J=8Hz), 6.83 (1H, s), 6.92-6.97 (2H, m), 7.04 (1H, d, J=8Hz), 7.47 (1H, t, J=8Hz), 7.91 (1H, d, J=8Hz), 8.02 (1H, d, J=8Hz), 8.30-8.35 (1H, m)

25 99) 3-Methoxy-N-methyl-N-[4-methyl-2-[5-(4-methylpiperazin-1-yl)carbonylpent-1-yloxy]phenyl]-4-(2-morpholinomethyl-1H-benzimidazole-4-yl)carbonylamino benzamide trihydrochloride

30 NMR (DMSO-d<sub>6</sub>, δ) : 1.41-1.52 (2H, m), 1.52-1.64 (2H, m), 1.72-1.80 (2H, m), 2.22 (3H, s), 2.40 (2H, t, J=8Hz), 2.73 (3H, s), 2.80-3.10 (4H, m), 3.18 (3H, s), 3.34-3.55 (7H, m), 3.80 (3H, s), 3.82-4.10 (6H, m), 4.37-4.45 (1H, m), 4.72 (2H, s), 6.64 (1H, d, J=8Hz), 6.82 (1H, s), 6.92-6.94 (2H, m), 7.03 (1H, d, J=8Hz), 7.46 (1H, t, J=8Hz), 7.90 (1H, d, J=8Hz), 8.03 (1H, d, J=8Hz), 8.30 (1H, d, J=8Hz)

## CLAIMS

1. A compound of the formula :



wherein

$R^1$  is aryl, cyclo(lower)alkyl or a heterocyclic group,  
 each of which may be substituted with substituent(s)  
 selected from the group consisting of halogen;  
 hydroxy; nitro; protected amino; amino; acyl;  
 substituted acyl; acyl(lower)alkylsulfinyl;  
 acyl(lower)alkylsulfonyl; acyloxy;  
 lower alkylamino(lower)alkylcarbamoxyloxy;  
 aryl; cyano; a heterocyclic group;  
 lower alkenyl optionally substituted with acyl,  
 substituted acyl, aryl or acyl-substituted aryl;  
 lower alkynyl optionally substituted with amino,  
 acylamino or substituted acylamino;  
 lower alkyl optionally substituted with halogen, amino,  
 lower alkylamino, acylamino, substituted acylamino,  
 hydroxy, acyloxy, acyl(lower)alkanoyloxy, acyl,  
 substituted acyl, acyl(lower)alkoxyimino, aryl or  
 acyl-substituted aryl;  
 lower alkylthio optionally substituted with acyl or  
 substituted acyl;  
 alkoxy optionally substituted with aryl, substituted  
 aryl, hydroxy, acyloxy, amino, lower alkylamino,  
 protected amino, a heterocyclic group, acyl-substituted  
 pyridyl, substituted acyl-substituted pyridyl, halogen,  
 acyl(lower)alkylamino, N-protected-acyl(lower)-

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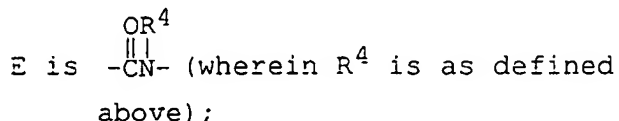
35

- alkylamino, N-acyl(lower)alkyl-N-lower alkylamino, acyl, substituted acyl, acylamino, substituted acylamino, lower alkylhydrazinocarbonylamino, hydroxyimino, acyl(lower)alkoxyimino, substituted
- 5 acyl(lower)alkoxyimino, acyl(lower)alkoxy, guanidino or N-protected guanidino; and lower alkenyloxy optionally substituted with acyl or substituted acyl;
- $R^2$  is hydrogen; lower alkyl optionally substituted with hydroxy, aryl or acyl; or cyclo(lower)alkyl;
- 10  $R^3$  is hydrogen; halogen; hydroxy; acyloxy; substituted acyloxy; lower alkyl optionally substituted with hydroxy or lower alkoxy; lower alkoxy optionally substituted with aryl, amino, protected amino, acyl, hydroxy, cyano or lower alkylthio; nitro; amino; acyl; substituted
- 15 acyl; or cyclo(lower)alkyloxy;
- A is a single bond, O or NH;
- E is lower alkylene, lower alkenylene,  $\text{-}\overset{\text{O}}{\parallel}\text{C-}$ ,  $\text{-}\overset{\text{O}}{\parallel}\text{S-}$ , or a group of the formula :
- 20  $\text{-G-J-}$
- in which G is lower alkylene or  $\text{-}\overset{\text{O}}{\parallel}\text{C-}$  and
- J is O or  $\text{-}\overset{\text{R}^4}{\underset{|}{\text{N}}}\text{-}$
- 25 (wherein  $R^4$  is hydrogen or N-protective group);
- X is  $\text{-CH=CH-}$ ,  $\text{-CH=N-}$  or S; and
- Y is aryl which may be substituted with acyl, protected amino(lower)alkanoyl, protected amino and nitro, amino and nitro or diamino;
- 30 or a condensed heterocyclic group which may be substituted with substituent(s) selected from the group consisting of halogen, acyl, lower alkoxy, hydroxy, guanidino, mercapto, acylamino, amino, a heterocyclic group, cyanoamino, amino(lower)alkyl(lower)alkylamino,
- 35 lower alkylamino, lower alkylamino(lower)alkylamino,

substituted-heterocyclic group, lower alkylhydrazino,  
aryloxy, lower alkylthio, aryl, protected amino,  
N-protected lower alkylamino(lower)alkylamino,  
N-protected amino(lower)alkyl(N'-lower alkyl)amino,  
5 amino(lower)alkyl(N-lower alkyl)amino, lower  
alkylamino(lower)alkyl(N-lower alkyl)amino, lower  
alkoxy(lower)alkylamino and lower alkyl optionally  
substituted with aryl, ar(lower)alkoxy, cyano,  
hydroxyimino, mercapto, lower alkylamino, acyloxy,  
10 halogen, lower alkoxy, protected hydroxy, hydroxy, lower  
alkoxyaryl, protected amino, amino, a heterocyclic group  
or substituted heterocyclic group;

provided that when Y is phenyl which may be substituted with  
lower alkyl or acyl,

15 then A is a single bond and



and pharmaceutically acceptable salt thereof.

20

2. A compound according to claim 1, wherein  
R<sup>1</sup> is aryl, cyclo(lower)alkyl or a heterocyclic group,  
each of which may be substituted with substituent(s)  
selected from the group consisting of halogen;  
25 hydroxy; nitro; amino; acyl; substituted acyl;  
acyl(lower)alkylsulfinyl; acyl(lower)alkylsulfonyl;  
acyloxy; lower alkylamino(lower)alkylcarbamoxyloxy;  
aryl; cyano; a heterocyclic group;  
lower alkenyl optionally substituted with acyl,  
30 substituted acyl, aryl or acyl-substituted aryl;  
lower alkynyl optionally substituted with amino,  
acylamino or substituted acylamino;  
lower alkyl optionally substituted with halogen, amino,  
lower alkylamino, acylamino, substituted acylamino,  
35 hydroxy, acyloxy, acyl(lower)alkanoyloxy, acyl,



- substituted acyl, acyl(lower)alkoxyimino, aryl or acyl-substituted aryl;  
 lower alkylthio optionally substituted with acyl or substituted acyl;
- 5 alkoxy optionally substituted with aryl, substituted aryl, hydroxy, acyloxy, amino, lower alkylamino, protected amino, a heterocyclic group, acyl-substituted pyridyl, substituted acyl-substituted pyridyl, halogen, acyl(lower)alkylamino, N-protected-acyl(lower)-
- 10 alkylamino, N-acyl(lower)alkyl-N-lower alkylamino, acyl, substituted acyl, acylamino, substituted acylamino, lower alkylhydrazinocarbonylamino, hydroxyimino, acyl(lower)alkoxyimino, substituted acyl(lower)alkoxyimino, acyl(lower)alkoxy, guanidino or
- 15 N-protected guanidino; and lower alkenyloxy optionally substituted with acyl or substituted acyl;
- $R^2$  is hydrogen; lower alkyl optionally substituted with hydroxy, aryl or acyl; or cyclo(lower)alkyl;
- $R^3$  is hydrogen; halogen; hydroxy; acyloxy; substituted
- 20 acyloxy; lower alkyl optionally substituted with hydroxy or lower alkoxy; lower alkoxy optionally substituted with aryl, amino, protected amino, acyl, hydroxy, cyano or lower alkylthio; nitro; amino; acyl; substituted acyl; or cyclo(lower)alkyloxy;
- 25 A is a single bond, O or NH;

E is lower alkylene, lower alkenylene,  $\begin{smallmatrix} \text{O} \\ \parallel \\ -\text{C}- \end{smallmatrix}$ ,  $\begin{smallmatrix} \text{O} & \text{O} \\ \parallel & \parallel \\ -\text{S}- & \end{smallmatrix}$ , or a group of the formula :

30  $-\text{G}-\text{J}-$

in which G is lower alkylene or  $\begin{smallmatrix} \text{O} \\ \parallel \\ -\text{C}- \end{smallmatrix}$  and

J is O or  $\begin{smallmatrix} \text{R}^4 \\ | \\ -\text{N}- \end{smallmatrix}$

(wherein  $R^4$  is hydrogen or N-protective group);

X is  $-\text{CH}=\text{CH}-$ ,  $-\text{CH}=\text{N}-$  or S; and

Y is aryl which is substituted with protected amino and  
nitro, amino and nitro or diamino; or a condensed  
5 heterocyclic group which may be substituted with  
substituent(s) selected from the group consisting of  
halogen, acyl, lower alkoxy, hydroxy, guanidino,  
mercapto, acylamino, amino and lower alkyl optionally  
substituted with lower alkylamino, acyloxy, halogen,  
10 lower alkoxy, protected hydroxy, hydroxy, lower  
alkoxyaryl, protected amino, amino or a heterocyclic  
group.

3. A compound according to claim 2, wherein  
15  $R^1$  is aryl which may be substituted with lower alkoxy  
substituted with acyl or acylamino,  
 $R^2$  is lower alkyl,  
 $R^3$  is hydrogen, lower alkyl or lower alkoxy,  
A is a single bond or NH,

20 E is  $\begin{array}{c} \text{O} \\ \parallel \\ -\text{C}- \end{array}$  or  $\begin{array}{c} \text{O} \\ \parallel \\ -\text{CNH}- \end{array}$ ,  
X is  $-\text{CH}=\text{CH}-$ , and  
Y is a condensed heterocyclic group which is substituted with  
lower alkyl optionally substituted with lower  
25 alkylamino, acyloxy, halogen, lower alkoxy, protected  
hydroxy, hydroxy, lower alkoxyaryl, protected amino,  
amino or a heterocyclic group.

4. A compound according to claim 3, wherein  
30  $R^1$  is phenyl or tolyl, each of which is substituted with  
lower alkoxy substituted with N-lower  
alkylpiperazinylcarbonyl,  
 $R^3$  is lower alkoxy,  
A is a single bond,

E is  $\begin{array}{c} \text{O} \\ \parallel \\ -\text{CNH}- \end{array}$ , and

Y is benzimidazol which is substituted with lower alkyl optionally substituted with amino, hydroxy or N-lower alkylpiperazinyl.

5

5. A compound according to claim 3, wherein

$R^1$  is phenyl or tolyl, each or which is substituted with lower alkoxy substituted with N-lower alkylpiperazinylcarbonyl,

10  $R^3$  is lower alkoxy,

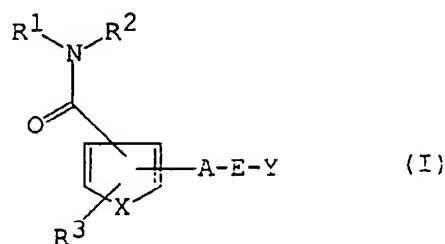
A is NH,

E is  $\begin{array}{c} \text{O} \\ \parallel \\ -\text{C}- \end{array}$ ,

15 Y is benzimidazolyl which is substituted with lower alkyl optionally substituted with amino, hydroxy or N-lower alkylpiperazinyl.

6. A process for preparing the formula :

20



25

wherein

$R^1$  is aryl, cyclo(lower)alkyl or a heterocyclic group, each of which may be substituted with substituent(s) selected from the group consisting of halogen; hydroxy; nitro; protected amino; amino; acyl; substituted acyl; acyl(lower)alkylsulfinyl; acyl(lower)alkylsulfonyl; acyloxy; lower alkylamino(lower)alkylcarbamoyloxy; aryl; cyano; a heterocyclic group; lower alkenyl optionally substituted with acyl,

35

- substituted acyl, aryl or acyl-substituted aryl;  
 lower alkynyl optionally substituted with amino,  
 acylamino or substituted acylamino;  
 lower alkyl optionally substituted with halogen, amino,  
 5 lower alkylamino, acylamino, substituted acylamino,  
 hydroxy, acyloxy, acyl(lower)alkanoyloxy, acyl,  
 substituted acyl, acyl(lower)alkoxyimino, aryl or  
 acyl-substituted aryl;  
 lower alkylthio optionally substituted with acyl or  
 10 substituted acyl;  
 alkoxy optionally substituted with aryl, substituted  
 aryl, hydroxy, acyloxy, amino, lower alkylamino,  
 protected amino, a heterocyclic group, acyl-substituted  
 pyridyl, substituted acyl-substituted pyridyl, halogen,  
 15 acyl(lower)alkylamino, N-protected-acyl(lower)-  
 alkylamino, N-acyl(lower)alkyl-N-lower alkylamino, acyl,  
 substituted acyl, acylamino, substituted acylamino,  
 lower alkylhydrazinocarbonylamino, hydroxyimino,  
 acyl(lower)alkoxyimino, substituted  
 20 acyl(lower)alkoxyimino, acyl(lower)alkoxy, guanidino or  
 N-protected guanidino; and lower alkenyloxy optionally  
 substituted with acyl or substituted acyl;  
 $R^2$  is hydrogen; lower alkyl optionally substituted with  
 hydroxy, aryl or acyl; or cyclo(lower)alkyl;  
 25  $R^3$  is hydrogen; halogen; hydroxy; acyloxy; substituted  
 acyloxy; lower alkyl optionally substituted with hydroxy  
 or lower alkoxy; lower alkoxy optionally substituted  
 with aryl, amino, protected amino, acyl, hydroxy, cyano  
 or lower alkylthio; nitro; amino; acyl; substituted  
 30 acyl; or cyclo(lower)alkyloxy;  
 A is a single bond, O or NH;  
 E is lower alkylene, lower alkenylene,  $\begin{array}{c} \text{O} \\ \parallel \\ -\text{C}- \end{array}$ ,  $\begin{array}{c} \text{O} \\ \parallel \\ -\text{S}- \\ \parallel \\ \text{C} \end{array}$ , or  
 a group of the formula :

in which G is lower alkylene or  $\text{-}\overset{\text{O}}{\underset{\text{||}}{\text{C}}}\text{-}$  and

J is O or  $\text{-}\overset{\text{R}^4}{\underset{|}{\text{N}}}\text{-}$

5 (wherein  $\text{R}^4$  is hydrogen or N-protective group);

X is  $\text{-CH=CH-}$ ,  $\text{-CH=N-}$  or S; and

Y is aryl which may be substituted with acyl, protected amino(lower)alkanoyl, protected amino and nitro, amino and nitro or diamino;

10 or a condensed heterocyclic group which may be substituted with substituent(s) selected from the group consisting of halogen, acyl, lower alkoxy, hydroxy, guanidino, mercapto, acylamino, amino, a heterocyclic group, cyanoamino, amino(lower)alkyl(lower)alkylamino, 15 lower alkylamino, lower alkylamino(lower)alkylamino, substituted-heterocyclic group, lower alkylhydrazino, aryloxy, lower alkylthio, aryl, protected amino, N-protected lower alkylamino(lower)alkylamino, N-protected amino(lower)alkyl(N'-lower alkyl)amino, 20 amino(lower)alkyl(N-lower alkyl)amino, lower alkylamino(lower)alkyl(N-lower alkyl)amino, lower alkoxy(lower)alkylamino and lower alkyl optionally substituted with aryl, ar(lower)alkoxy, cyano, hydroxyimino, mercapto, lower alkylamino, acyloxy, 25 halogen, lower alkoxy, protected hydroxy, hydroxy, lower alkoxyaryl, protected amino, amino, a heterocyclic group or substituted heterocyclic group;

provided that when Y is phenyl which may be substituted with lower alkyl or acyl,

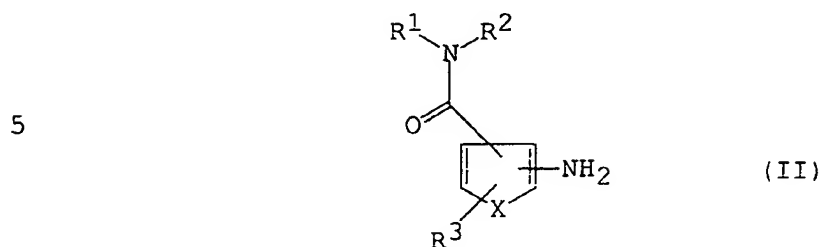
30 then A is a single bond and

E is  $\text{-}\overset{\text{OR}^4}{\underset{|||}{\text{CN}}}\text{-}$  (wherein  $\text{R}^4$  is as defined above);

or pharmaceutically acceptable salt thereof,

35 which comprises,

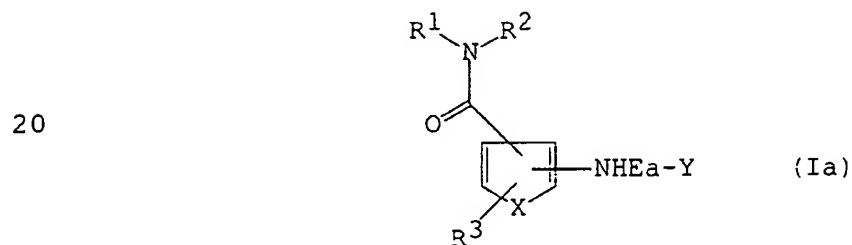
1) reacting a compound of the formula :



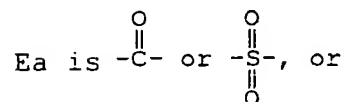
or its salt with a compound of the formula :



or its reactive derivative at the carboxy group or the sulfo group, or a salt thereof to provide a compound of the formula :



25 or its salt, in the above formulas,  
 $R^1$ ,  $R^2$ ,  $R^3$ , X and Y are each as defined above, and

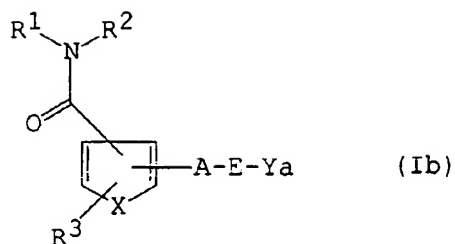


30

2) reacting a compound of the formula :

35

5



(Ib)

10

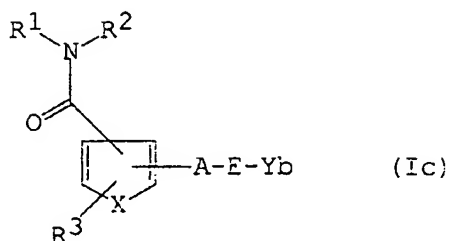
or its salt with a compound of the formula :



in the presence of a base to provide a compound of the formula :

15

20



(Ic)

25

or its salt, in the above formulas,

$\text{R}^1$ ,  $\text{R}^2$ ,  $\text{R}^3$ , A, E and X are each as defined above,

Ya is indolyl,

$\text{R}^5$  is lower alkyl,

$\text{Z}^1$  is an acid residue, and

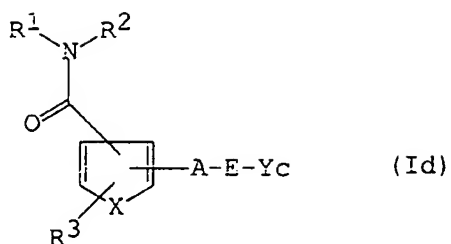
30

Yb is N-(lower alkyl)indolyl, or

3) subjecting a compound of the formula :

35

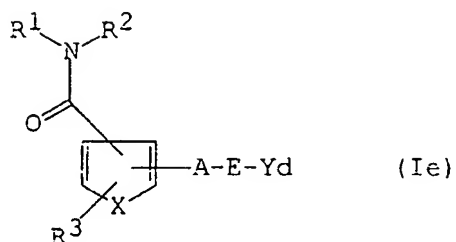
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or its salt to reduction to provide a compound of the formula :

15



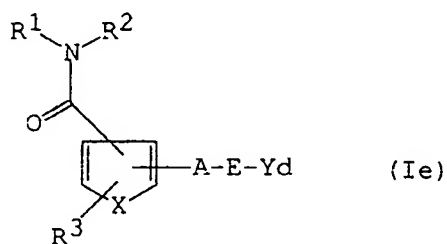
20

or its salt, in the above formulas,  
 R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, A, E and X are each as defined above,  
 Yc is phenyl substituted with amino and nitro, and  
 Yd is phenyl substituted with diamino,

25

4) reacting a compound of the formula :

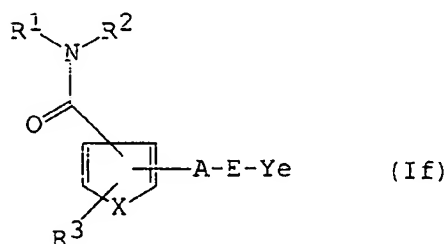
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35



or its salt with aroyl halide,  
 cyano(lower)alkylcarboxylic acid,  
 mercapto(lower)alkylcarboxylic acid, lower alkylactone,  
 1,1-dihalo-1,1-diphenoxymethane, diphenyl  
 5 N-sulfamoylcarbonimide, diphenyl N-cyanocarbonimide,  
 dicyandiamide, 1,1'-thiocarbonylimidazole, cyanogen  
 bromide, lower alkoxycarbonyl isothiocyanate,  
 tri(lower)alkyl orthoformate, tetra(lower)alkyl  
 orthoformate, lower alkylcarboxylic acid,  
 10 halo(lower)alkylcarboxylic acid, protected  
 amino(lower)alkylcarbonyl halide or  
 a heterocyclic(lower)alkylcarbonyl halide to provide a  
 compound of the formula :

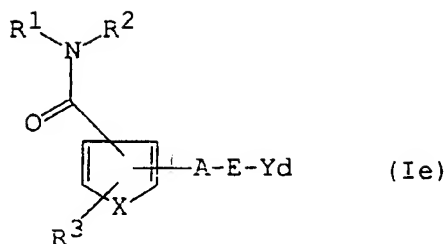


or its salt, in the above formulas,  
 R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, A, E, X and Yd are each as defined above,  
 and

Ye is benzimidazolyl optionally 2-position substituted  
 25 with aryl, phenoxy, sulfamoylamino, cyanoamino,  
 guanidino, mercapto, amino, lower  
 alkoxycarbonylamino, lower alkoxy or lower alkyl  
 optionally substituted with cyano, mercapto,  
 hydroxy, halogen, protected amino or a heterocyclic  
 30 group, or

5) reacting a compound of the formula :

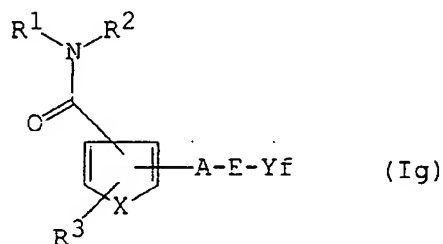
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or its salt with glyoxal and sodium hydrogen sulfite, or  
sodium nitrite to provide a compound of the formula :

15



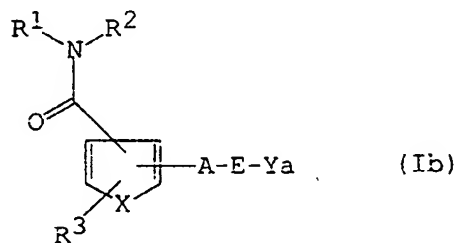
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or its salt, in the above formulas,  
R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, A, E, X and Yd are each as defined above,  
and  
Yf is quinoxaliny1 or benzotriazolyl, or

25

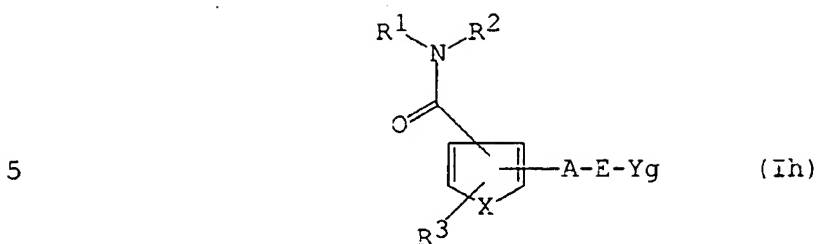
6) reacting a compound of the formula :

30



or its salt with an acylating agent to provide  
a compound of the formula :

35

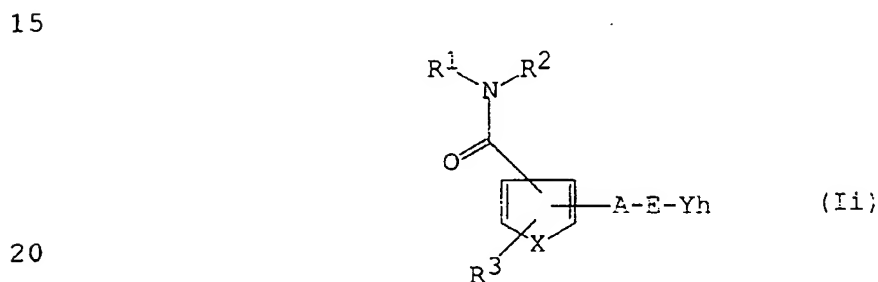


or its salt, in the above formulas,

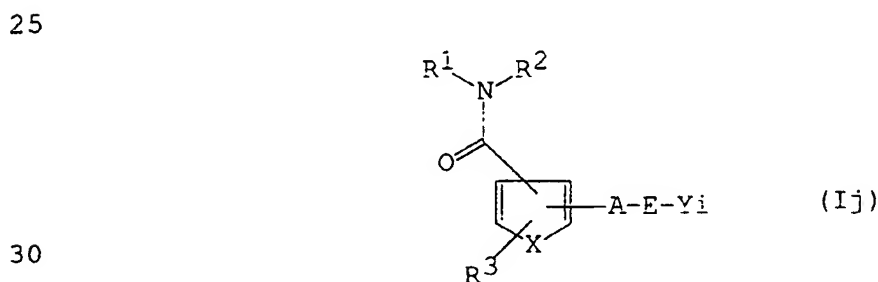
10  $R^1$ ,  $R^2$ ,  $R^3$ , A, E, X and Ya are each as defined above,  
and

Yg is N-acylindolyl, or

7) subjecting a compound of the formula :



or its salt to elimination reaction of the N-substituent  
group to provide a compound of the formula :



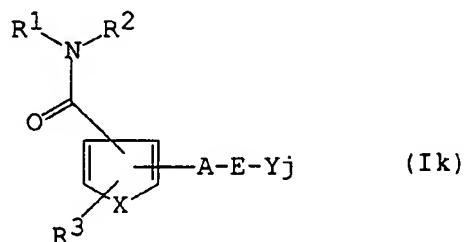
or its salt, in the above formulas,

35  $R^1$ ,  $R^2$ ,  $R^3$ , A, E and X are each as defined above,  
Yh is (N-acyl)acylindolinyl, N-acylindolinyl,

(N-acyl)hydroxy(lower)alkylindolinyl, lower  
 alkylamino(lower)alkylamino(N-acyl)indolinyl,  
 (N-lower alkoxyarylmethyl)acylbenzimidazolyl,  
 (N-lower alkoxycarbonyl)phthalimido(lower)-  
 5 alkylindolyl, N-protected lower alkylamino(lower)-  
 alkylamino(N-acyl)benzimidazolyl,  
 (N-acyl)benzimidazolyl, (N-acyl)(lower)-  
 alkylbenzimidazolyl, N-protected  
 amino(lower)alkyl(N-lower alkyl)amino(N-  
 10 acyl)benzimidazolyl, N-acylindolyl,  
 (N-acyloxymethyl)indolyl,  
 (N-acyl)acylindolyl, (N-arylmethyl)lower  
 alkoxy(lower)alkylbenzimidazolyl or (N-lower  
 alkoxyarylmethyl)acylbenzimidazolyl; and  
 15 Yi is acylindolinyl, indolinyl,  
 hydroxy(lower)alkylindolinyl,  
 lower alkylamino(lower)alkylaminoidolinyl,  
 acylbenzimidazolyl, phthalimido(lower)alkylindolyl,  
 amino(lower)alkylindolyl,  
 20 lower alkylamino(lower)alkylaminobenzimidazolyl,  
 benzimidazolyl, lower alkylbenzimidazolyl,  
 amino(lower)alkyl(N-lower  
 alkyl)aminobenzimidazolyl, indolyl, acylindolyl,  
 lower alkoxy(lower)alkylbenzimidazolyl or  
 25 acylbenzimidazolyl;

8) subjecting a compound of the formula :

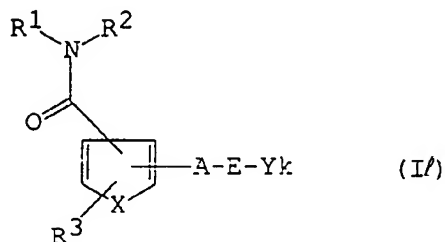
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35

or its salt to elimination reaction of the N-protective group to provide a compound of the formula :

5



10

or its salt, in the above formulas,

$R^1$ ,  $R^2$ ,  $R^3$ , A, E and X are each as defined above,

$Y_j$  is aryl which is substituted with protected amino and

15

nitro; or a condensed heterocyclic group which is

substituted with protected amino or lower alkyl

substituted with protected amino; and

$Y_k$  is aryl which is substituted with amino and nitro; or

a condensed heterocyclic group which is substituted

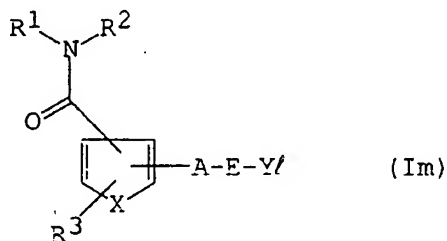
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with amino or lower alkyl substituted with amino;

or

9) subjecting a compound of the formula :

25

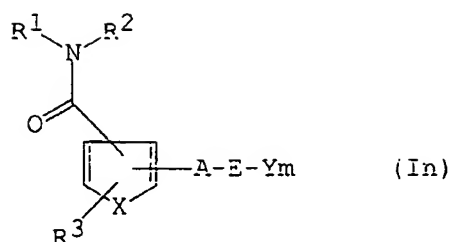


30

or its salt to deesterification reaction to provide a compound of the formula :

35

5



or its salt, in the above formulas,

$R^1$ ,  $R^2$ ,  $R^3$ , A, E and X are each as defined above,

10

$Y_0$  is aryl substituted with esterified carboxy, or a condensed heterocyclic group substituted with esterified carboxy, and

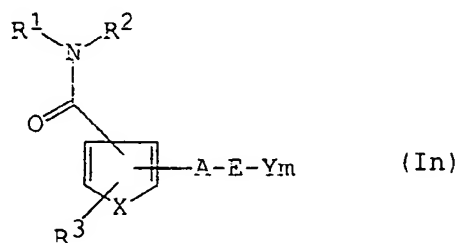
$Y_m$  is aryl substituted with carboxy, or a condensed heterocyclic group substituted with

15

carboxy, or

10) reacting a compound of the formula :

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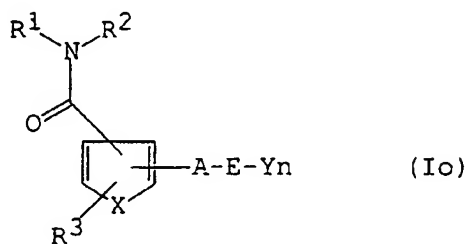


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or its reactive derivative at the carboxy group

or a salt thereof with an amine or its salt to provide a compound of the formula :

30



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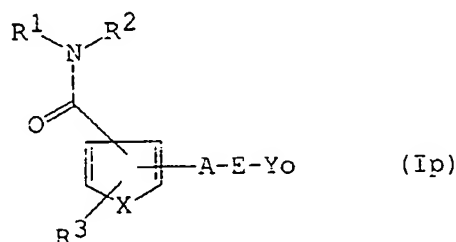
or its salt, in the above formulas,

$R^1$ ,  $R^2$ ,  $R^3$ , A, E, X and  $Y_m$  are each as defined above,

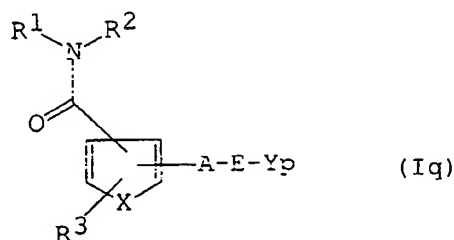
and

$Y_n$  is aryl or a condensed heterocyclic group, each of which is substituted with substituted or unsubstituted N-containing heterocycliccarbonyl, carbamoyl, heterocycliccarbamoyl, or substituted or unsubstituted lower alkylcarbamoyl; or

11) subjecting a compound of the formula :



or its salt to elimination reaction of methyl or the hydroxy-protective group to provide a compound of the formula :



or its salt, in the above formulas,

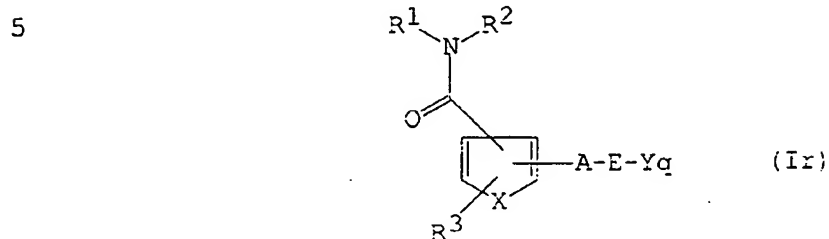
$R^1$ ,  $R^2$ ,  $R^3$ , A, E and X are each as defined above,

$Y_o$  is a condensed (N-acyl)N-containing heterocyclic group or a condensed heterocyclic group, each of which is substituted with methoxy or lower alkyl substituted with protected hydroxy; and

$Y_p$  is a condensed (N-acyl)N-containing heterocyclic group or a condensed heterocyclic group, each of which is substituted with hydroxy or lower alkyl

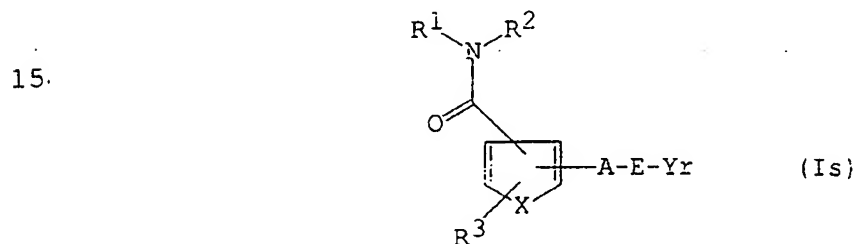
substituted with hydroxy; or

12) reacting a compound of the formula :



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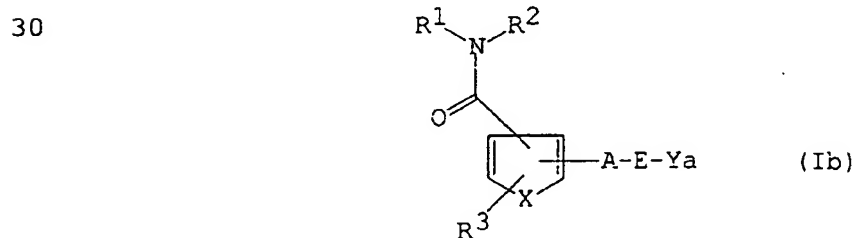
or its salt with an acylating agent to provide a compound of the formula :



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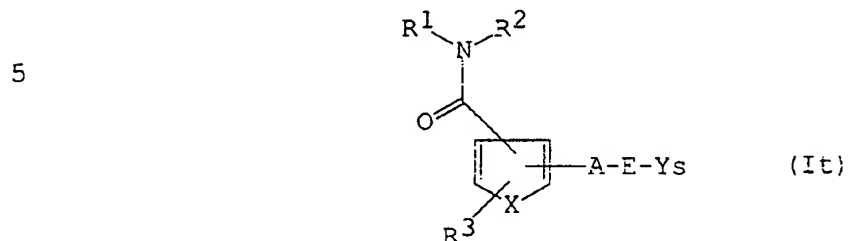
or its salt, in the above formulas,  
 $R^1$ ,  $R^2$ ,  $R^3$ , A, E and X are each as defined above,  
 $Yq$  is a condensed heterocyclic group which is  
substituted with amino or amino(lower)alkyl, and  
 $Yr$  is a condensed heterocyclic group which is  
substituted with acylamino or  
25 acylamino(lower)alkyl, or

13) reacting a compound of the formula :





or its salt with N-lower alkylmethyleammonium halide  
to provide a compound of the formula :

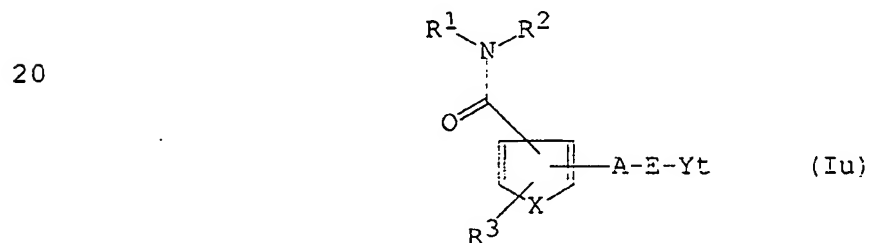


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or its salt, in the above formulas,  
 $R^1$ ,  $R^2$ ,  $R^3$ , A, E, X and Ya are each as defined above,  
and

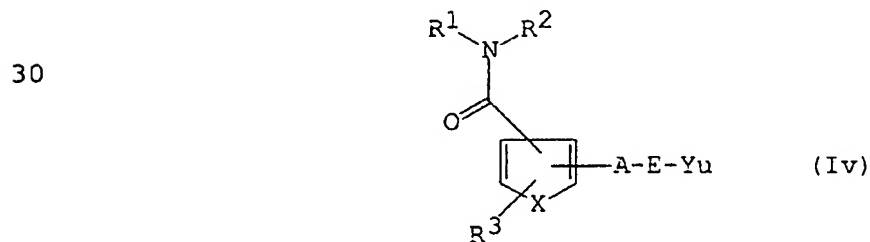
15 Ys is indolyl which is substituted with methyl  
substituted with lower alkylamino, or

14) subjecting a compound of the formula :



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or its salt to oxidation reaction to provide a compound  
of the formula :



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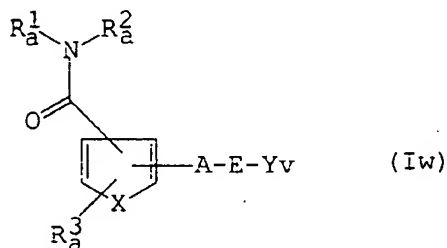
or its salt, in the above formulas,

$R^1$ ,  $R^2$ ,  $R^3$ , A, E and X are each as defined above,

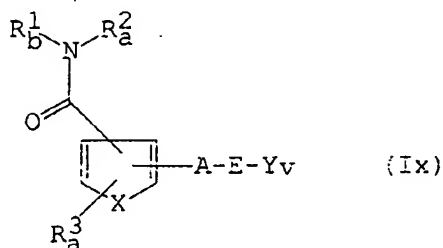
Yt is a condensed heterocyclic group which is  
substituted with lower alkyl substituted with  
hydroxy, and

Yu is a condensed heterocyclic group which is  
substituted with lower alkyl substituted with  
formyl, or

15) subjecting a compound of the formula :



or its salt to deesterification reaction to provide a  
compound of the formula :



or its salt, in the above formulas,

A, E and X are each as defined above,

$R_a^1$  is aryl substituted with esterified carboxy or lower  
alkoxy substituted with esterified carboxy,

$R_b^1$  is aryl substituted with carboxy or lower alkoxy  
substituted with carboxy,

$R_a^2$  is lower alkyl,

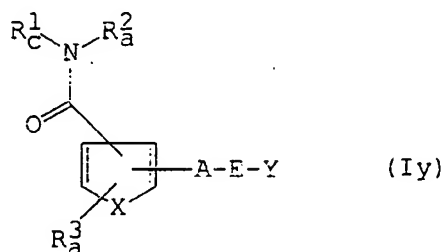
$R_a^3$  is hydrogen or lower alkoxy, and

Yv is benzimidazolyl optionally substituted with lower alkyl or protected amino(lower)alkyl, or

16) subjecting a compound of the formula :

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10

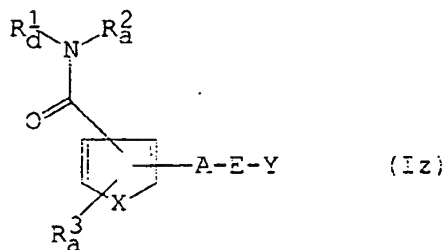


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or its salt to elimination reaction of methyl substituted with aryl or substituted aryl to provide a compound of the formula :

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25

or its salt, in the above formulas,

$R_a^2$ ,  $R_a^3$ , A, E, X and Y are each as defined above,

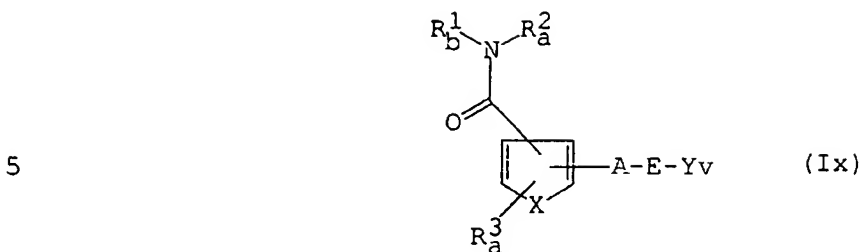
30

$R_C^1$  is aryl substituted with methoxy which is substituted with substituted or unsubstituted aryl, and

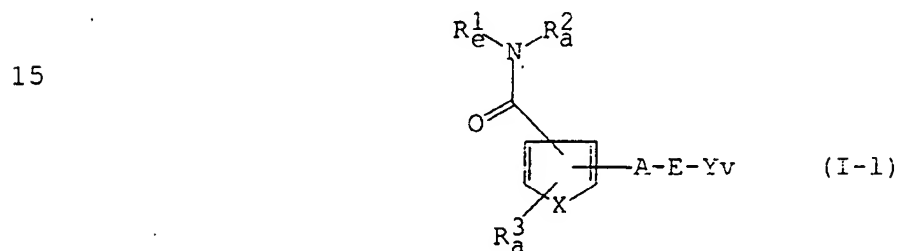
$R_D^1$  is aryl substituted with hydroxy, or

17) reacting a compound of the formula :

35



10 or its reactive derivative at the carboxy group or a salt thereof with an amine or its salt to provide a compound of the formula :



20

or its salt, in the above formulas,

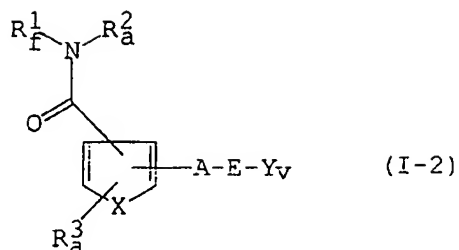
$R^1_b$ ,  $R^2_a$ ,  $R^3_a$ , A, E, X and Yv are each as defined above,  
and

25  $R^1_e$  is aryl substituted with N-protected piperazinylcarbonyl, oxopiperidinylcarbonyl, carbamoyl, lower alkylcarbamoyl, lower alkylaminocarbamoyl or lower alkylamino(lower)-alkyl(N-lower)alkylcarbamoyl, or aryl which is substituted with lower alkoxy substituted with

30 N-protected piperazinylcarbonyl, oxopiperidinylcarbonyl, carbamoyl, lower alkylcarbamoyl, lower alkylaminocarbamoyl or lower alkylamino(lower)alkyl(N-lower)alkylcarbamoyl,

35 18) reacting a compound of the formula :

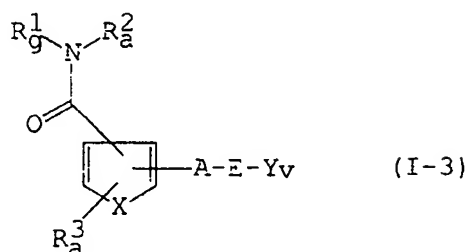
5



10

or its salt with a reducing agent to provide a compound of the formula :

15



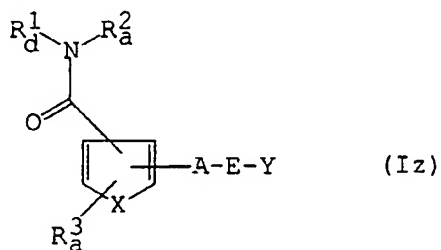
20

or its salt, in the above formulas,  
 R<sup>2</sup><sub>a</sub>, R<sup>3</sup><sub>a</sub>, A, E, X and Y<sub>v</sub> are each as defined above,  
 R<sup>1</sup><sub>f</sub> is aryl which is substituted with lower alkoxy  
 substituted with oxopiperidinylcarbonyl, and  
 R<sup>1</sup><sub>g</sub> is aryl which is substituted with lower alkoxy  
 substituted with hydroxypiperidinylcarbonyl, or

25

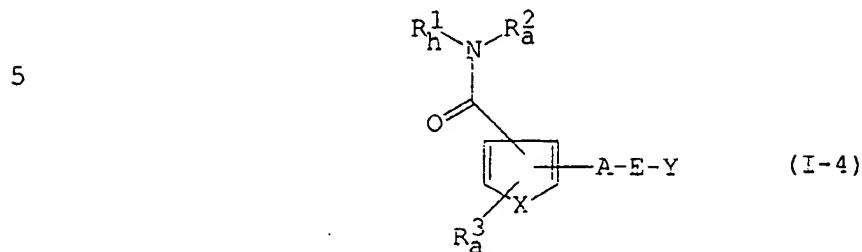
19) reacting a compound of the formula :

30



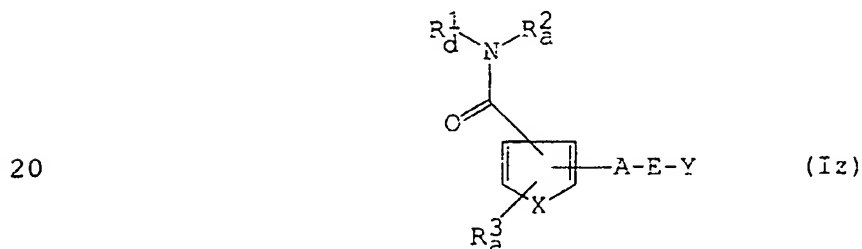
35

or its salt with an acylating agent to provide a compound of the formula :



10 or its salt, in the above formulas,  
 $R_h^1$ ,  $R_a^2$ ,  $R_a^3$ , A, E, X and Y are each as defined above,  
 and  
 $R_h^1$  is aryl substituted with acyloxy, or

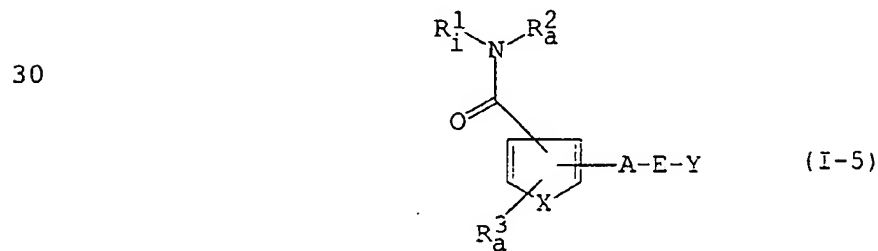
15 20) reacting a compound of the formula :



or its salt with a compound of the formula :



to provide a compound of the formula :



or its salt, in the above formulas,

$R_a^1$ ,  $R_a^2$ ,  $R_a^3$ , A, E, X and Y are each as defined above,

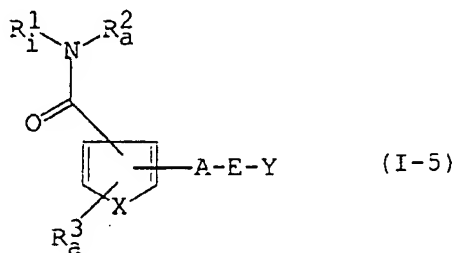
$R_i^1$  is aryl which is substituted with lower alkoxy  
substituted with protected amino,

5  $R^6$  is lower alkyl substituted with protected amino, and

$Z^2$  is an acid residue, or

21) subjecting a compound of the formula :

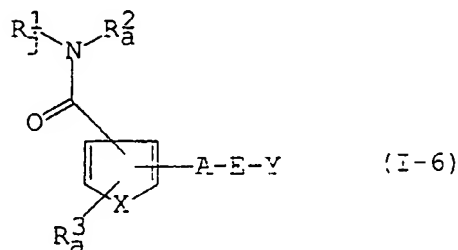
10



15

or its salt to elimination reaction of N-protective  
group to provide a compound of the formula :

20



25

or its salt, in the above formulas,

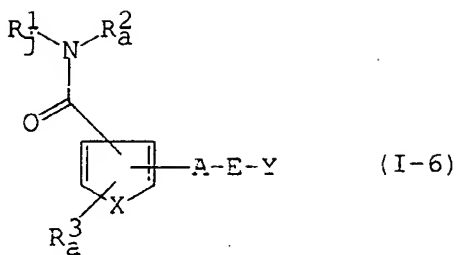
$R_i^1$ ,  $R_a^2$ ,  $R_a^3$ , A, E, X and Y are each as defined above,  
and

30  $R_j^1$  is aryl which is substituted with lower alkoxy  
substituted with amino, or

22) reacting a compound of the formula :

35

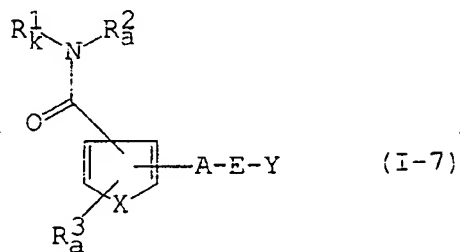
5



10

or its salt with an acylating agent to provide a compound of the formula :

15



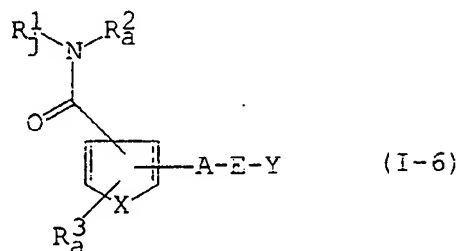
20

or its salt, in the above formulas,  
 $R^1_j$ ,  $R^2_a$ ,  $R^3_a$ , A, E, X and Y are each as defined above,  
 and  
 $R^1_k$  is aryl which is substituted with acylamino, or

25

23) reacting a compound of the formula :

30



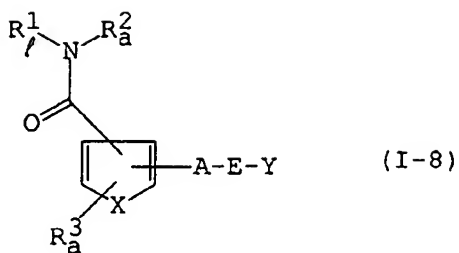
35

or its salt with lower alkanal in the presence of a reducing agent to provide a compound of the formula :



315

5



10

or its salt, in the above formulas,

$R_j^1$ ,  $R_a^2$ ,  $R_a^3$ , A, E, X and Y are each as defined above,

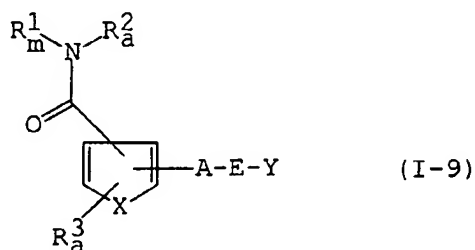
and

$R_j^1$  is aryl which is substituted with lower alkylamino,  
or

15

24) subjecting a compound of the formula :

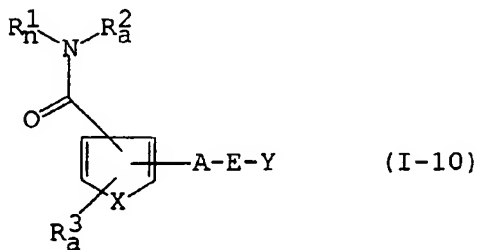
20



25

or its salt to reduction to provide a compound of the  
formula :

30



35

or its salt, in the above formulas,

$R_a^2$ ,  $R_a^3$ , A, E, X and Y are each as defined above,

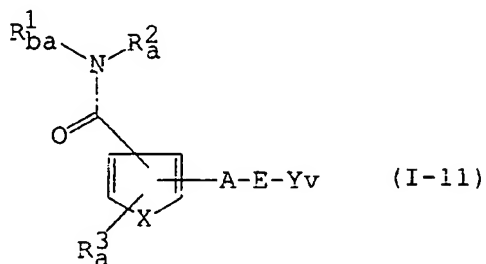
316

$R_m^1$  is aryl substituted with nitro, and  
 $R_n^1$  is aryl substituted with amino, or

25) reacting a compound of the formula :

5

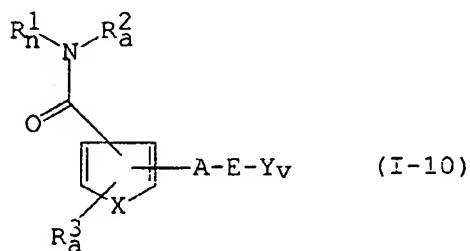
10



15

or its salt with an azide compound to provide a compound  
of the formula :

20



25

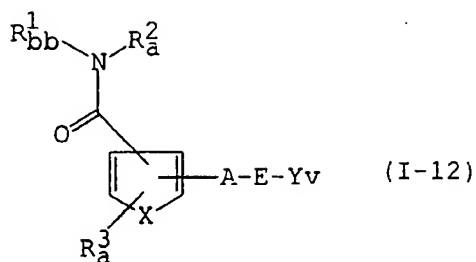
or its salt, in the above formulas,  
 $R_n^1$ ,  $R_a^2$ ,  $R_a^3$ , A, E, X and Yv are each as defined above,  
and  
 $R_{ba}^1$  is aryl substituted with carboxy, or

30

26) reacting a compound of the formula :

35

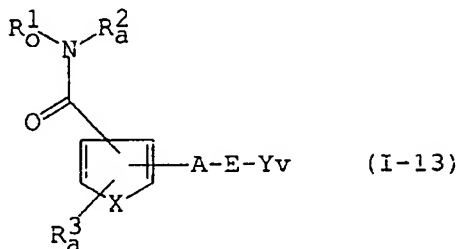
5



10

or its reactive derivative at the carboxy group or a salt thereof with a reducing agent to provide a compound of the formula :

15



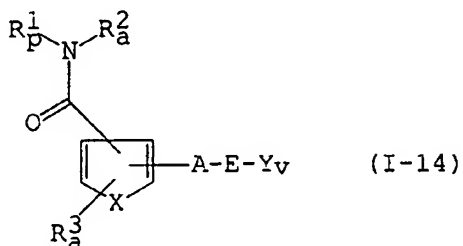
20

or its salt, in the above formulas,  
 $R_a^2$ ,  $R_a^3$ , A, E, X and Yv are each as defined above,  
 $R_{bb}^1$  is aryl which is substituted with lower alkoxy substituted with carboxy, and  
 $R_O^1$  is aryl which is substituted with lower alkoxy substituted with hydroxymethyl, or

25

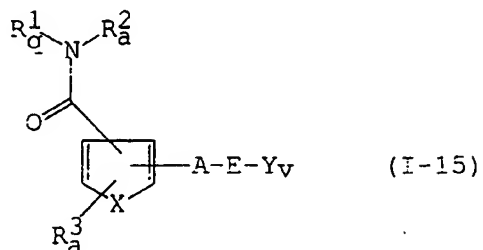
27) reacting a compound of the formula :

30



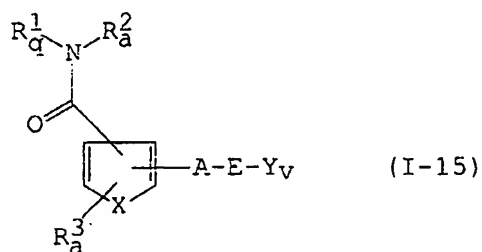
35

or its salt with an acylating agent to provide a compound of the formula :

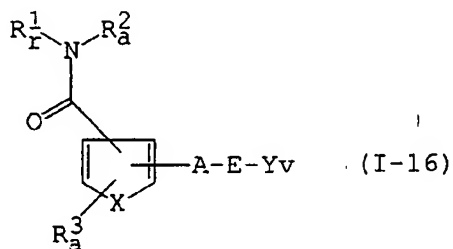


10 or its salt, in the above formulas,  
 $R^2_a$ ,  $R^3_a$ , A, E, X and Yv are each as defined above,  
 $R^1_p$  is aryl which is substituted with lower alkoxy  
 substituted with hydroxy, and  
 15  $R^1_q$  is aryl which is substituted with lower alkoxy  
 substituted with acyloxy, or

28) reacting a compound of the formula :



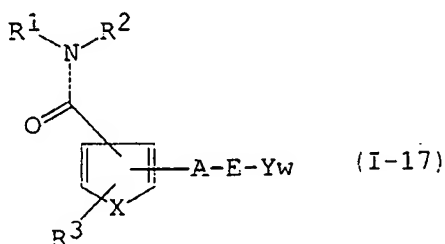
or its salt with an alkali metal salt of phthalimide to provide a compound of the formula :



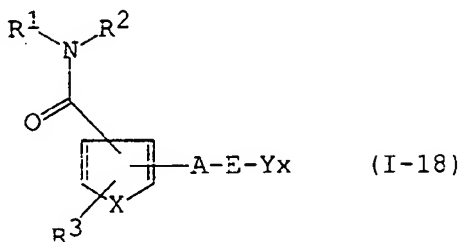
or its salt, in the above formulas,  
 $R_Q^1$ ,  $R_A^2$ ,  $R_A^3$ , A, E, X and Yv are each as defined above,  
 and

$R_F^1$  is aryl which is substituted with lower alkoxy  
 5 substituted with phthalimido, or

29) reacting a compound of the formula :

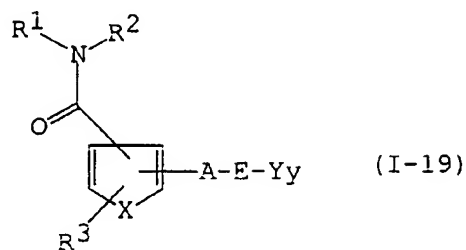


15  
 or its salt with an amine to provide a compound of the  
 formula :

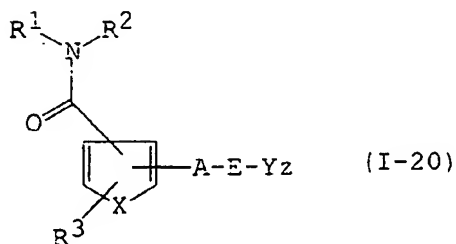


25  
 or its salt, in the above formulas,  
 $R^1$ ,  $R^2$ ,  $R^3$ , A, E and X are each as defined above,  
 Yw is benzimidazolyl substituted with halogen, and  
 Yx is benzimidazolyl substituted with N-lower  
 30 alkylpiperidyl, morpholino, lower alkylamino,  
 di(lower)alkylaminopiperidino,  
 di(lower)alkylhydrazino,  
 amino(lower)alkyl(N-lower alkyl)amino or  
 di(lower)alkylamino(lower)alkylamino, or

30) subjecting a compound of the formula :



10 or its salt to elimination reaction of N-protective group to provide a compound of the formula :



20

or its salt, in the above formulas,

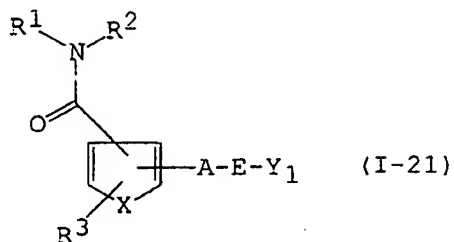
R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, A, E and X are each as defined above,

Yy is benzimidazolyl substituted with N-protected piperidyl, and

25

Yz is benzimidazolyl substituted with piperidyl, or

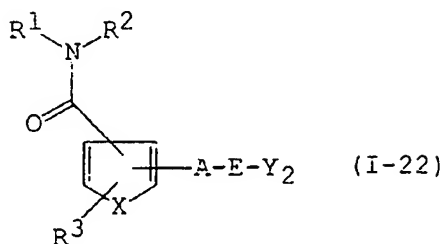
31) reacting a compound of the formula :



35

or its salt with hydroxylamine or its salt to provide a compound of the formula :

5



10

or its salt, in the above formulas,

$R^1$ ,  $R^2$ ,  $R^3$ , A, E and X are each as defined above,

$Y_1$  is benzimidazolyl or indolyl, each of which is

15

substituted with formyl or cyano(lower)alkyl, and

$Y_2$  is benzimidazolyl or indolyl, each of which is

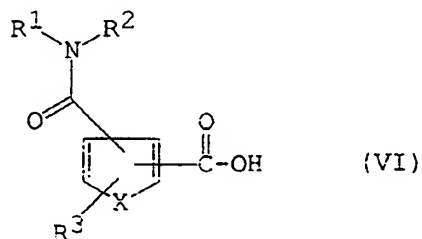
substituted with hydroxyiminomethyl or

amino(hydroxyimino) (lower)alkyl, or

20

32) reacting a compound of the formula :

25



30

or its reactive derivative at the carboxy group

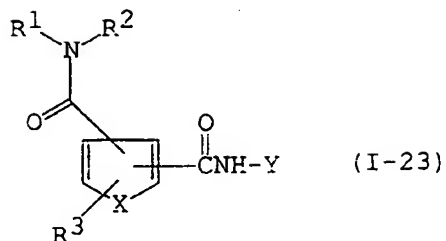
or a salt thereof with a compound of the formula :



35

or its salt to provide a compound of the formula :

5



10

or its salt, in the above, formulas,  
R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, X and Y are each as defined above.

15

7. A pharmaceutical composition comprising a compound of claim 1, as an active ingredient, in association with a pharmaceutically acceptable, substantially non-toxic carrier or excipient.

8. A compound of claim 1 for use as a medicament.

20

9. A method of therapeutic treatment and/or prevention of hypertension, heart failure, renal insufficiency, edema, ascites, vasopressin parasecretion syndrome, hepatocirrhosis, hyponatremia, hypokalemia, diabetic, circulation disorder, cerebrovascular disease, Meniere's syndrome or motion sickness which comprises administering an effective amount of a compound of claim 1 to human beings or animals.

25

30

10. Use of a compound of claim 1 for the manufacture of a medicament for treating and/or preventing hypertension, heart failure, renal insufficiency, edema, ascites, vasopressin parasecretion syndrome, hepatocirrhosis, hyponatremia, hypokalemia, diabetic, circulation disorder, cerebrovascular disease, Meniere's syndrome or motion sickness in human beings or animals.

35



# INTERNATIONAL SEARCH REPORT

International Application No

PCT/JP 97/04192

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D235/08 A61K31/415 A61K31/40 C07D235/14 C07D235/30  
C07D209/08 C07D209/42 C07D235/12 C07D235/24 C07D235/06  
C07D235/10 C07D235/26 C07D209/12 C07D401/04 C07D401/06

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 91 05549 A (OTSUKA PHARMA CO LTD) 2 May 1991 cited in the application see pages 216-221; examples 120-127, 129, and 130 see page 343; example 374 see pages 479-480; examples 613 and 614 ---	1,2,7-10
X	EP 0 640 592 A (AMERICAN CYANAMID CO) 1 March 1995 see page 55; table I, the compounds of the examples 123 and 124 ---	1,2,7-10
X	EP 0 636 625 A (AMERICAN CYANAMID CO) 1 February 1995 see pages 188-189; table XIII, the compounds of the examples 484 and 485 ---	1,2,7-10
	--- -/--	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

25 February 1998

Date of mailing of the international search report

03. 04. 98

Name and mailing address of the ISA

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Authorized officer

Fink, D

# INTERNATIONAL SEARCH REPORT

Internal Application No

PCT/JP 97/04192

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 29152 A (FUJISAWA PHARMACEUTICAL CO ;SETOI HIROYUKI (JP); OHKAWA TAKEHIKO ( ) 2 November 1995 cited in the application see page 233 - page 234; claim 1	1,7-10
Y	see the whole document	1-10
Y	WO 95 34540 A (OTSUKA PHARMA CO LTD ;OGAWA HIDENORI (JP); KONDO KAZUMI (JP); YAMA) 21 December 1995 see pages 634-639, claim 1; and in particular, page 636, lines 12-15 therein	1-10
X	DE 28 02 023 A (SANDOZ AG) 3 August 1978 see page 14 - page 15; examples 10,17	1-3,7,8
X	Y.G. PERRON ET AL.: "Derivatives of 6-Aminopenicillanic Acid. III. Reactions with N-Substituted Phthalamic Acids" JOURNAL OF MEDICINAL AND PHARMACEUTICAL CHEMISTRY., vol. 5, September 1962, EASTON US, pages 1016-1025, XP002056852 see page 1019; table II, compound no. 10	1,2
X	CHEMICAL ABSTRACTS, vol. 90, no. 21, 21 May 1979 Columbus, Ohio, US; abstract no. 168396r, M.T. NGUYEN: "Synthesis of indole ketoamides." page 583; column 1; XP002056856 see abstract; and Chemical Abstracts, CHEMICAL SUBSTANCES, 10th Collective Index, vol. 86-95, 1977-1981, page 4185CS, the compound with the RN: '69971-86-4! & TAP CHI HOA HOC, vol. 16, no. 1, 1978, pages 26-29,	1,2
X	T. YAMAZAKI ET AL.: "Dipolar Addition and Acyl Migration in Reactions of Benzyne and Acetylenes with 5-Membered Ring $\alpha$ -Diazo Ketones" TETRAHEDRON LETTERS., no. 44, October 1972, OXFORD GB, pages 4533-4536, XP002056853 see page 4535, the compound no. 31.	1,2

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## INTERNATIONAL SEARCH REPORT

International Application No

PCT/JP 97/04192

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>CHEMICAL ABSTRACTS, vol. 108, no. 13, 28 March 1988 Columbus, Ohio, US; abstract no. 112144e, M.A.I. SALEM ET AL.: "Reaction of 3-carbethoxy-5,6-benzocoumarin with anthranilic acid and synthesis and some reactions of 3-(3',1'-benzoxazin-4'-one)-5,6-benzocouma rin." page 599; column 1; XP002056857 see abstract; and Chemical Abstracts, CHEMICAL SUBSTANCES, 12th Collective Index, vol. 106-115, 1987-1991, page 57433CS: the compound with the RN: '113120-43-7! &amp; J. CHEM. SOC. PAK., vol. 9, no. 1, 1987; pages 177-189, ---</p>	1,2
X	<p>CHEMICAL ABSTRACTS, vol. 119, no. 21, 22 November 1993 Columbus, Ohio, US; abstract no. 225895w, M.R. SELIM ET AL.: "Synthesis of some benzoxazin-4-one derivatives and study of their reaction with nucleophilic reagents." page 1009; column 1; XP002056858 see abstract; and Chemical Abstracts, CHEMICAL SUBSTANCES, 13th Collective Index, vol. 116-125, 1992-1996, book 11, page 410: the compound with the RN: '150711-88-9! &amp; J. INDIAN CHEM. SOC., vol. 69, no. 10, 1992, pages 688-690, ---</p> <p style="text-align: center;">-/--</p>	1,2

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/JP 97/04192

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>CHEMICAL ABSTRACTS, vol. 93, no. 1, 7 July 1980 Columbus, Ohio, US; abstract no. 8105d, M.M. ABDALLA ET AL.: "Synthesis of some 3-(3',1'-benzoxazin-4'-one)-6- substituted coumarins and their chemical reactions." page 745; column 1; XP002056859 see abstract; in particular the compounds of formula I, wherein R = H, and R1 = PhNH, 4-MeOC6H4NH, and 4-MeC6H4NH &amp; EGYPT. J. CHEM., vol. 20, no. 3, 1979, pages 245-257,</p>	1,2
X	<p>A. VARNAVAS ET AL.: "Anthranoyl-anthranilic acid: a template for the development of a new class of cholecystokinin receptor ligands" PHARMAZIE., vol. 51, no. 10, October 1996, BERLIN DD, pages 697-700, XP002056854 see page 698; table 1, the compounds no. 7 and 14</p>	1,2
X	<p>M.-F. GRENIER-LOUSTALOT ET AL.: "Mechanics and Kinetics of Polymerization of Thermoplastic Polyimides. II. Study of "Bridged" Dianhydride/Aromatic Amine Systems" JOURNAL OF POLYMER SCIENCE, POLYMER CHEMISTRY EDITION., vol. 31, no. 12, November 1993, NEW YORK US, pages 3049-3063, XP002056855 see page 3050; the compound no. 5, wherein X = C=O</p>	1

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/JP 97/04192

### Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
see FURTHER INFORMATION sheet PCT/ISA/210
2. ☒ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

### Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

#### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

**FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

Claims Nos.: 1,2,6-10

because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Claims 1 and 2 are so broad that for determining the scope of a meaningful International Search due account has been taken of Rule 33.3 PCT; special emphasis was put on the following subject-matter:  
The compounds of claims 3-5, the methods of their preparation, pharmaceutical compositions containing them, and their use as medicaments

Remark : Although claim 9 is directed to a method of treatment of the human/animal body , the search has been carried out and based on the alleged effects of the compound/composition.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

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